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Saturated fatty acid intakes and the risk of myocardial infarction in women: a prospective cohort

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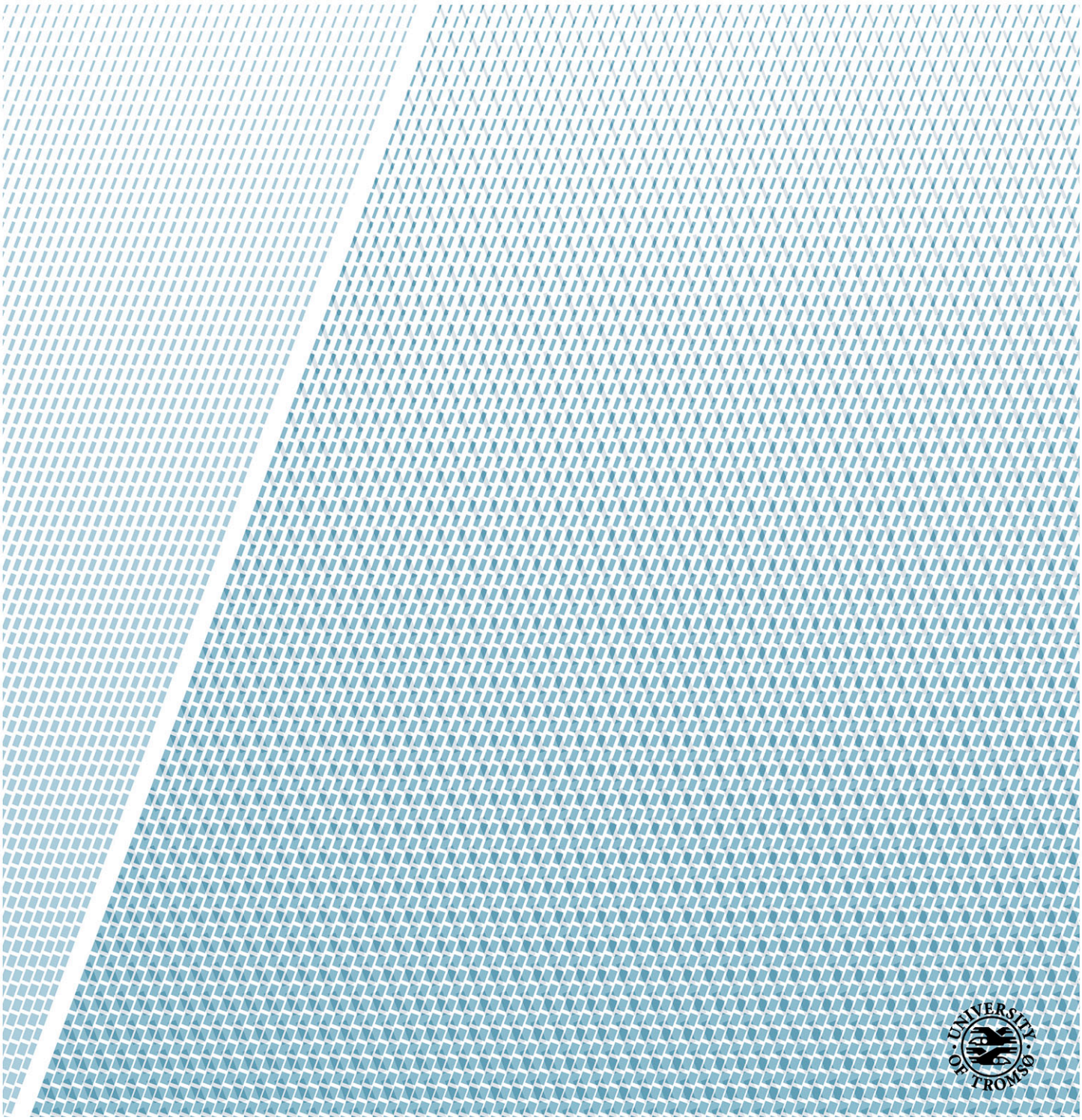

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Abstract

Background: Some recent researches about relationships between dietary fat and the risk of cardiovascular disease revealed contrasting results with the lipid hypothesis. The primary object of this study was to explore the risk of non-fatal (self-reported) myocardial infarction in relation to saturated fat consumption. We used food frequency questionnaire (FFQ) to measure saturated fat intake.

Method: We used prospective cohort design and analysis data from 60,203 women aged 41-70 years at recruitment, participating in the Norwegian Women and Cancer (NOWAC) study. All participants answered a 6-8 page questionnaire that contains the FFQ together with questions on health and lifestyle questionnaires. We excluded 377 women who reported myocardial infarction at the study baseline. The consumption of saturated fat (SFA) was divided into four groups by quartile. Saturated fat intake was ordered from lowest to highest consumption of saturated fat and was divided into four equal parts. The 1^{st} quartile, the 25^{th} percentile, is in other word, the lowest saturated fat consumption group. The data point above 75^{th} percentile, which is highest saturated fat consumption group, is our reference group. The relationship between SFAs consumption and the time to first self-reported myocardial infarction was used in analysis by Cox proportional hazard model. The following covariates, age, body mass index, smoking status, physical activity and the use of hypertensive medicine were adjusted for in the analysis. In addition

we also estimate the impact of SFA intake on MI incidence separately according to BMI statues to clarify whether BMI modified the association between SFA intake and MI incidence.

Results: An increased risk of myocardial infarction was observed in the 25th percentile saturated fat intake group (hazard ratio (HR) =1.33, 95% confidence interval (CI) = 1.02 - 1.74) than reference group (Above the 75th percentile saturated fat intake). The 50th percentile saturated fat intake group is 1.06 times as likely to have myocardial infarction but it was not statistically significant (95%CI= 0.80-1.40). The 75th percentile saturated fat intake group also had increased risk of myocardial infraction compared to the reference group (HR=1.24, 95% CI=0.92-1.58). When we stratified according to BMI categories, however, a lowest SFA intake did not shown an increased relative risk of MI. It was not significant. A decreased risk tendency was found in the lowest SFA intake category among underweight (BMI ≦ 20) women group (BMI ≦ 20: HR=0.64, 95% CI= 0.21-1.98) and this tendency was same in the 3rd SFA intake category (BMI ≦ 20: HR=0.68, 95% CI = 0.26-1.75). An increased risk tendency of MI was still found in the lowest SFA intake group among normal (BMI 20.01-24.99 : HR=1.50, 95% CI=0.99-2.26) ,overweight(BMI 25-29.99: HR=1.54, 95% CI=0.99-2.41) and obese(BMI≧ 30: HR=1.10, 95% CI=0.53-2.29) groups. However it was not significant. In NOWAC study, the association between SFA intake and the risk of MI incidence did not observed.

Conclusion: This study suggests that there may be no association between saturated fat intake and the risk of non-fatal myocardial infarction. The 25th percentile group of

saturated fat intake showed increased risk for non-fatal myocardial infarction during a mean follow-up period of 6.12 years. However, there is a possibility that this result might have been influenced by the effect of confounding factors.

Keywords: dietary fats, saturated fatty acids, cardiovascular disease, cholesterol, and myocardial infarction.

Abbreviations

BMI = body mass index

CVDs= cardiovascular disease

CHD= coronary heart disease

CI = confidence interval

24-HDR= 24-hour dietary recall

DALY= disability-adjusted life year

HDL-C = high -density lipoprotein cholesterol

HR= hazard ratio

LDL-C = low- density lipoprotein cholesterol

MUFAs= monounsaturated fatty acids

NCDs = non-communicable diseases

PUFAs = polyunsaturated fatty acids

SFAs= saturated fatty acids

TFAs= trans fatty acids

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1 INTRODUCTION

1.1 Background

Public health action to prevent cardiovascular disease (CVD) is very important because CVD is one of the most significant causes of premature deaths in the world (2). CVDs include diseases of the heart, vascular disease of the brain, and diseases of the blood vessels. CVDs are the leading cause of non-communicable diseases (NCDs) and are responsible for a large proportion of global mortality and disability(3). In 2008, about 17.3 million people died due to CVD-related causes. About 30% of global mortality and 10% of global disease burden, expressed in Disability–adjusted life years (DALYs), are attributed to CVD(2). The percentage of males and females in the global CVD burden expressed in DALYs due to ischemic heart disease is 45% and 37% respectively. Ischemic heart disease or coronary artery disease were due to atherosclerosis and hypertension (2).

Monitoring the incidence and mortality of myocardial infarction (MI) plays a pivotal role in the understanding of CVD and in estimating the public health burden. Both high-income countries and low-and middle-income countries have similar public health problems and challenges because of CVD with ageing population. Nonetheless, the incidence of MI in high-income countries has diminished considerably due to the combination of population wide primary prevention and individual health care approaches (2-6).

Through government wide actions and policies, the strategy for primary MI prevention has focused on reducing established risk factors, such as high blood pressure, high serum cholesterol as well as low- density lipoprotein cholesterol (LDL-C), physical inactivity, high blood sugar and smoking. Several findings in various studies suggest that modified dietary fat intake together with healthy life styles prevents MI (7-10). The term modified fat diets is used where "the proportion of saturated fat is replaced by unsaturated fats and total fat intakes do not alter", while low fat diets are "where total fat is reduced and energy is usually replaced by increasing carbohydrate intake" (9).

In the prevention of cardiovascular disease, life style modification including a reduction in dietary saturated fat has been widely accepted through the lipid hypothesis (11-13). Previous studies suggested that there is a correlation between high dietary saturated fat and serum cholesterol increase. Studies also showed that high cholesterol level increases the risk of CVDs. However, the association between dietary saturated fat and the risk of CVD has not been consistently demonstrated in recent studies. Some studies have shown that reduced saturated fat in diets have no effect on CVD risk and the accuracy of the association of saturated fat with cardiovascular disease could be a subject of debate with numerous controversial views. (14-16). The purpose of this research is to estimate the association between dietary saturated fat intake and the risk of non-fatal myocardial infarction through a prospective epidemiologic study: The Norwegian Women and Cancer (NOWAC) study.

1.2 The types of fat and different types of fat in food

Lipid is an organic compound, including fats, oils and waxes, that does not readily dissolve in water but soluble in non-polar solvents. Lipid is a chemical term for fat and equivalently used for fat, wax, and oil. Fat is a macronutrient and essential for normal body function. Fats provide energy, pad the body's organs, insulate the body, maintain the body temperature and form cell membranes. They carry fat-soluble vitamins: vitamins A, D, E, and K, and also help in the absorption and storage of vitamins (17, 18).

There are three primary types of fat, they are: triglycerides, phospholipids, and sterols. 95% of dietary fat comes from triglycerides that are a major form of lipid in food and in the body. Phospholipids are type of fats that allow fats and water to mixed and constitute a small portion of dietary fat. The prototypical sterol is cholesterol, and sterols in the body include vitamin D, sex hormones, and cortisol. Triglycerides are composed of one molecule of glycerol combined with three molecules of fatty acids and are efficient in energy storing (19).

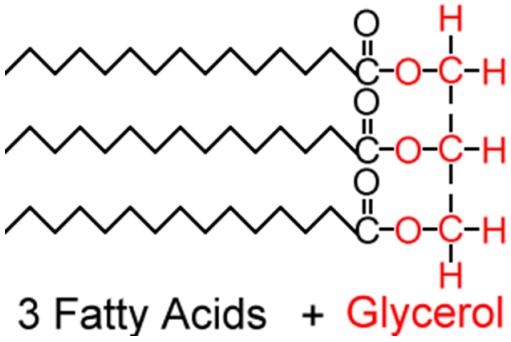


Figure 1-1Triglycerider: adopted from Frank et al., 2015 (1)

Fatty acids are long chains of carbon and hydrogen. There are two types of fatty acid, which are, saturated fatty acid and unsaturated fatty acid. Saturated fatty acids contains no double bonds while unsaturated fatty acids have one or more double bonds between the carbon atoms (20).

Saturated fatty acids (SFAs) are solid at room temperature. Animal product, butter, palm and coconuts oils, cheese, lard, tallow, and red meat are usually considered rich sources of SFAs. Studies have shown that SFAs raise the total and LDL-C level. (21)

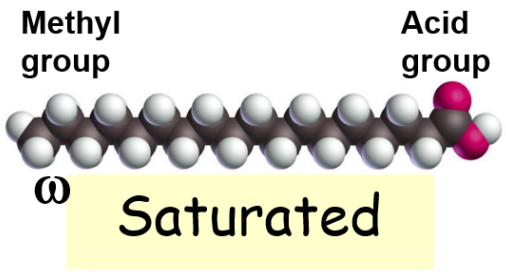
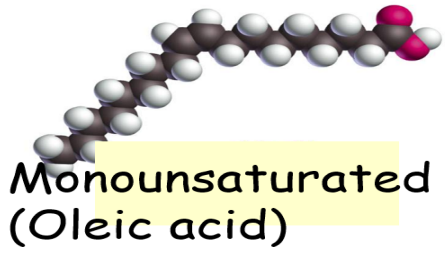


Figure 1-2 Saturated fatty acid: adopted from Frank et al., 2015 (1)

Monounsaturated fats (MUFAs) are liquid at room temperature and are present in plant food, such as nuts, avocados, and vegetable oils. Most of the monounsaturated fats help to lower the total and LDL-C level (21).

Polyunsaturated fatty acids (PUFAs) include omega-3 fatty (n-3 PUFAs) acids and omega-6 fatty acids (n-6 PUFAs). Plants such as many seeds, nuts, safflower oil, maize oil, cottonseed oil, sunflower oil, and soybean oil and fatty fish such as salmon, tuna, and



mackerels are rich in PUFAs. When saturated fats are replaced with PUFAs, especially omega-3 fatty acids, HDL-C level are raised and LDL-C are lowered (22).

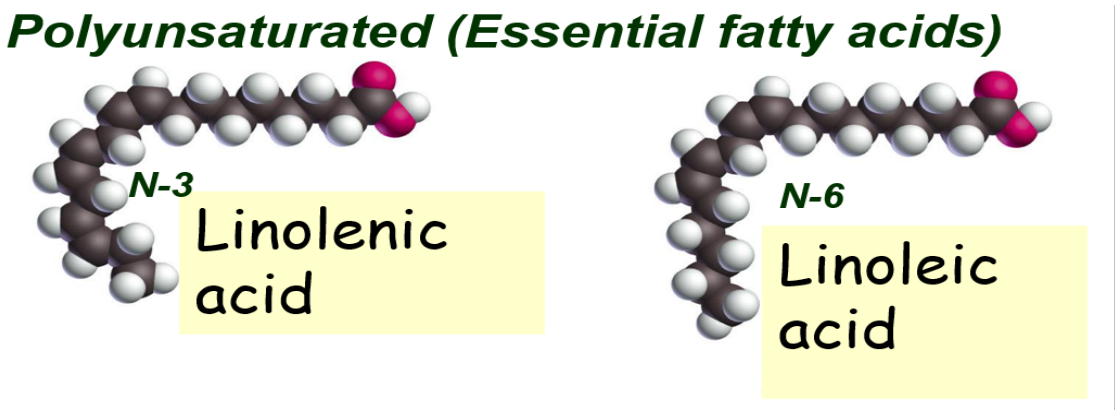


Figure 1-4 Polyunsaturated fatty acid: adopted from Frank et al., 2015 (1)

Trans fatty acid (TFA) is unsaturated fatty acid that contain double bonds in the E (trans) configuration. TFA is derived from hydrogenation process that converts vegetable oils to semisolid fats in the form of margarines through an industrial process, and manufactured form of trans fat is found in bakery product, fried food, crackers, cookies and doughnuts (22, 23). Recent studies report that the trans fats from hydrogenated oils is associated with increased risk of CVD due to raise LDL-C level and lowering HDL-C level. (14, 23).

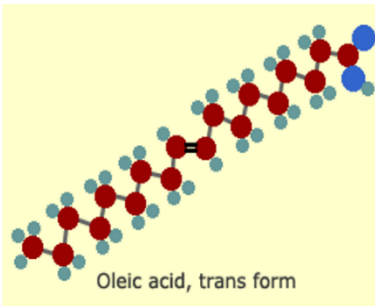


Figure 1-5Trans fatty acid: adopted from Frank et al., 2015 (1)

1.3 Literature review

A broad literature search was conducted to assess the relation between dietary fat intake and cardiovascular disease. The search was conducted through the Cochrane Library, MEDLINE, PubMed, Thomson ISI´s Web of Science, and Google Scholar in May 2015 updated till October 2015. The key words and the Medical Subject Heading (MeSH) terms were dietary fats, cardiovascular disease, fatty acids, cholesterol, and myocardial infarction. The references of relevant studies and reviews were further checked.

Dietary recommendations concerning dietary fat intake to prevent cardiovascular disease are established from Lipid hypothesis theory (11). Lipid hypothesis describe that atherosclerosis begins with damage to the endothelium caused by high blood pressure, smoking, or high cholesterol. That damage leads to the formation of plaque. Populations considered high risk are usually advised to reduce the intake of food rich in saturated fat. Both reducing the intake of saturated fat and increasing polyunsaturated fat intake have been an important dietary guideline for decades.

In 1957, Ancel Keys launched the Seven Countries Study (SCS) to examine the relationship between the dietary data, especially dietary fat, lifestyle, other risk factors and the rate of coronary heart disease and stroke in populations. It was designed as a cross-cultural prospective study that included more than 12,000 middle-age men in 16 cohorts in seven different countries: United States of America, Italy, Greece, Yugoslavia, Netherlands, Finland, and Japan.

The SCS study provided evidence that confirmed the lipid hypothesis that establishes an association between high serum cholesterol levels due to high intake of saturated fats, and coronary atherosclerosis.

If the lipid hypothesis is true, high saturated fat intake would elevate the total and/or LDL cholesterol and should be associated with an increased risk of cardiovascular diseases, while people with low cholesterol levels, who have reduced total and/or LDL cholesterol should have a lower risk of cardiovascular disease(24).

Earlier studies emphasized dietary changes and healthy lifestyle with the goal of decreasing the serum cholesterol level as a means of preventing CVD (12, 25, 26). There was however no consistent evidence showing the correlation between lowering blood cholesterol level and the decrease in the risk of coronary heart disease from those studies. Some dietary prevention trials showed that low fat diet was mostly effective in reducing serum cholesterol but had no impact on the incidence of myocardial infarction or stroke in contrast to a Mediterranean diet. The Mediterranean diet was defined around early 1960s, and is the traditional dietary pattern of the population groups in several countries that live around the Mediterranean Basin. This dietary pattern is characterized by abundant plant food such as vegetables, fruits, whole grain cereals, nuts and legumes, olive oil as main source of dietary fat, high consumptions of fish and low to moderate consumption of wine during meals (27, 28). The population is this region were shown by the SCS studies, as well as other studies, to have low levels of coronary heart disease (12, 13, 25, 29). Other studies showed that replacing saturated fats with polyunsaturated fatty acids such as omega 3 fatty acid, were likely to reduce the risk of myocardial infarction.

A systematic review carried out by Hopper (2001) on reduced or modified dietary fat for preventing cardiovascular disease found that modification of dietary fat could make a potentially important reduction in cardiovascular risk even though it was small. The recent systematic review of Hooper et al ´s (2011) reports that reducing saturated fat by reducing and/or modifying dietary fat can decrease the risk of cardiovascular events by 14% (9, 30). Several studies have shown evidence of the important relationship between saturated fat intake and the risk of coronary heart disease (26, 31). However, some other reviews and meta-analysis maintained that an association between saturated fatty acid and the risk of CVD remains unclear (14-16), while some have shown no association between dietary saturated fats and the risk of cardiovascular disease (14).

The report from the recent study by Dr Rajiv Chowdhury in Cambridge University titled 'Association of Dietary, Circulating, and Supplement Fatty Acids with Coronary Risk ' which appears in the journal 'Annals of Internal Medicine' also present contrasting findings. The study carried out a systematic review and meta- analysis of data from 72 studies involving a total of 600,000 participants in 18 countries. The findings of this study show that there is a non-significant association between the intake of ω-6 polyunsaturated fatty acids / total saturated fats and the risk of coronary heart disease(14).

Nonetheless, nutritional expert Dr. Willlet disagrees with the Chowdhury´s study result stating that it is misleading because of the omission of relevant data from some other studies, and he also cited errors in the data analysis in relation to ω-6 polyunsaturated fat.

Dietary fats, especially the saturated fats, are currently a very contentious issue but despite this, dietary guidelines in many countries hold that saturated fat should be limited to 10% of daily calorie, and trans fats limited to less than 1% because those fats increase the LDL

cholesterol level in the blood. This is based on the belief that high intake of saturated fats and trans fatty acids contribute to the risk of CVDs (32).

1.4 The importance of diet and lifestyle in relation to prevention of myocardial infarction

There are different kinds of risk factors in the prevention and development of CVD. The reasons that diet and life style are crucial factors in public health prevention are because these factors are changeable and manageable when compared with genetic factors. Mortality from cardio vascular disease in Norway has been reducing recently even though it is still the main cause of death(5). The Norwegian Myocardial Infarction Registry was established in 2012 as a national quality registry that provides information of treatments and a 30-day mortality rate for patients with myocardial infarctions admitted into Norwegian hospitals (5). Overall acute myocardial infarction (AMI) event rate in Norway started to decline from 2002 after a fluctuating period from 1994 to 2002. AMI event rates during 2002 to 2009 declined by 2.0 % in men and 2.1% in women annually (33). This trend could be partly explained by changes in different risk factors of first myocardial infarction. However it is not possible to fully explain the trend because of a complex relationship between different risk factors. Decline in smoking rate in men and women and improvement of medical treatment in hypertension and hyperlipidemia could have positively influenced this trend. Obesity, diet, physical activity, alcohol consumption, and psychosocial factors are also important risk factors.(7)

Dr Willet who is professor of Medicine at Harvard Medical School opined that genetic factors are not primarily responsible for different types of cancer or heart disease but diet and life style. His argument is supported by the several studies among immigrant populations(34-36). For instance, the mortality and/or mobility of cardiovascular disease among immigrant groups who moved from their home countries to other countries usually changed due to their adoption of new life style and diet of the host populations. Robertson et al (1977) reported that the incidence rate of CHD was twice as high among Japanese men in Hawaii, as in Japanese men in Japan ($P< 0.01$). There was a higher incidence rate of CHD among Japanese male immigrant in California than in Hawaii(34). Malin et al (2006) also reported differences in CHD mortality risk between immigrants in Sweden compared with populations living in their country of birth. The risk of CHD mortality among Southern European immigrants in Sweden was higher than in their countries of birth, and the risk of CHD among immigrants from Finland and Hungary in Sweden was lower than in their countries of birth. One of the possible explanations for different CHD rates among these immigrants may be the adoption of Swedish and US diet which is based on meat and dairy products (34-36).

In respects to reducing risk of CVD, dietary change is considered a highly cost-effective method. The substitution of saturated fat with nut oil was associated with 45% reduction in the risk of Coronary Heart Disease (CHD) from the data in the Nurses' Health Study (37). A pooled analysis of 11 cohort studies by Jokobsen et al (2009) showed that the risk of CVD events decreased 13% by the substitution of 5 % SFA with PUFAs (38), while the systematic review of Hoper et al (2012) reported reduction of saturated fat in diet reduces the risk of cardiovascular events by 14% (9).

"A healthy diet teamed with regular exercise and not smoking can eliminate 80 percent of heart disease and the majority of cancer cases" (39). It seems the healthy diet and lifestyle is more effective than any medicine. Thus, what the healthy diet is and how to give the right dietary advice to people without confusion is necessary. Recommendations for dietary fat in the prevention of cardiovascular disease should be based not only on evidence-based data about reduction of saturated fat, but also on the effects of the macronutrient replacing saturated fat in the diet.

1.5 The Norwegian Women and Cancer (NOWAC) study

The Norwegian Women and Cancer (NOWAC) study originally started in 1991 to explore the risk factors for breast cancer, with special focus on combined oral contraceptives (OCs) use. The study was further expanded to include other cancers, chronic illnesses and mortality in a prospective manner. Since the establishment of the cohort in 1991, 2 or 3 follow-up surveys have been conducted to collect information at an interval of 4-6 years(40-42). This thesis uses data collected from participants recruited in the period of 1996- 1997, 1998, and 2003 and the follow- up years in 2002, 2004-2005 and 2011.

1.6 Outline of the study

This thesis is organized in five chapters

Chapter 1 is the introduction to the study. It contains the background of study and reviews of relevant previous literatures in the area of the current study.

Chapter 2 presents the aim of the study with research hypothesis.

Chapter 3 describes the materials used to achieve the aim of this study and relevant statistical analysis of the data from the chosen study population.

Chapter 4 presents the results of the study in relation to the relationship between saturated fat intake and myocardial infarction and summarizes the study.

Chapter 5 discusses the findings of the study and methodological considerations.

Chapter 6 is the conclusions and future perspective

2 AIMS

The aim of this thesis is to examine the association between fat intake and the risk of myocardial infarction in a cohort of the Norwegian Women and Cancer (NOWAC) study. In this study, we shall focus on association between saturated fats intake and time to the occurrence of myocardial infarction.

The specific objective is to;

1. To assess the relation between saturated fatty acids and the risk of self-reported non-fatal myocardial infarction in women.

2.1 Research Hypotheses

1. High saturated fats in the diet increase the risk of myocardial infarction among women.

2.2 Research questions

What is the relationship between the intake of SFAs and the incidence of non-fatal myocardial infarction?

We divided the saturated fat intake into four equal groups by quartile. The data is ordered from lowest to highest the intake of saturated fat. 1^{st} quartile (Q1= 25^{th} percentile) split off the lowest 25% of data. 2^{nd} quartile (Q2= 50^{th} percentile) is until the median of data set and the last cut point is Q3 (=75_{th} percentile). We test our hypothesis by investigating the association between saturated fat intake and the risk of total incident myocardial

infarction. Saturated fat intake was used firstly as continuous variable and then as categorical variable.

3 MATERIALS AND METHODS

3.1 The Norwegian Women and Cancer (NOWAC) study.

The dataset used for this study was obtained from the Norwegian Women and Cancer (NOWAC) study through the Data and Publication Committee of the Department of Community Medicine of UiT-The Arctic University of Norway. The research is conducted by a quantitative method with a prospective study methodology.

The Norwegian Women and Cancer Study is a national population-based cohort study. 172,526 Norwegian women were recruited for the study over a period of 11 years (from 1991 to 2006). Participants were sampled randomly from the National Central Person Registry in Norway (42, 43). The national identity number was used in sampling and the follow-up information of cancer and death registries, and immigration information was obtained from Statistics Norway (SSB). To maintain participants´ confidentiality, the 11-digit national personal number was replaced with a serial number. Information was collected by the postal questionnaire that contains food frequency questionnaire (FFQ) section, together with health and lifestyle questionnaires. Each Participant received a letter of invitation with the explanation for the aim of the study and, a 6-8 page questionnaire and a pre-paid return envelope. Through the first enrollment, each of them were asked to tick ´yes´ if they agreed to take part in the study and return the questionnaire in the envelope provided. Subsequently, in the second and the third enrollment the questionnaire was sent only to participants who previously agreed in the informed consent to be a part of the study and answered the set of dietary questions (44). Questionnaires were returned to

the Institute of community medicine, University of Tromsø, Norway. Questionnaires were examined in the use of OCs and hormone replacement, age at menarche, menopause status, family history of breast Cancer, smoking, physical activity, alcohol consumption, height and weight, self-reported diseases, and social class. Detailed information on sunbathing habits and dietary habits was collected through FFQ (42). Appendix 1 contains sample of the questionnaires from series 39 which were enrolled over the period from 2004 to 2005.

An overview of the enrolment of the NOWAC cohort is shown in Figure 3-1.

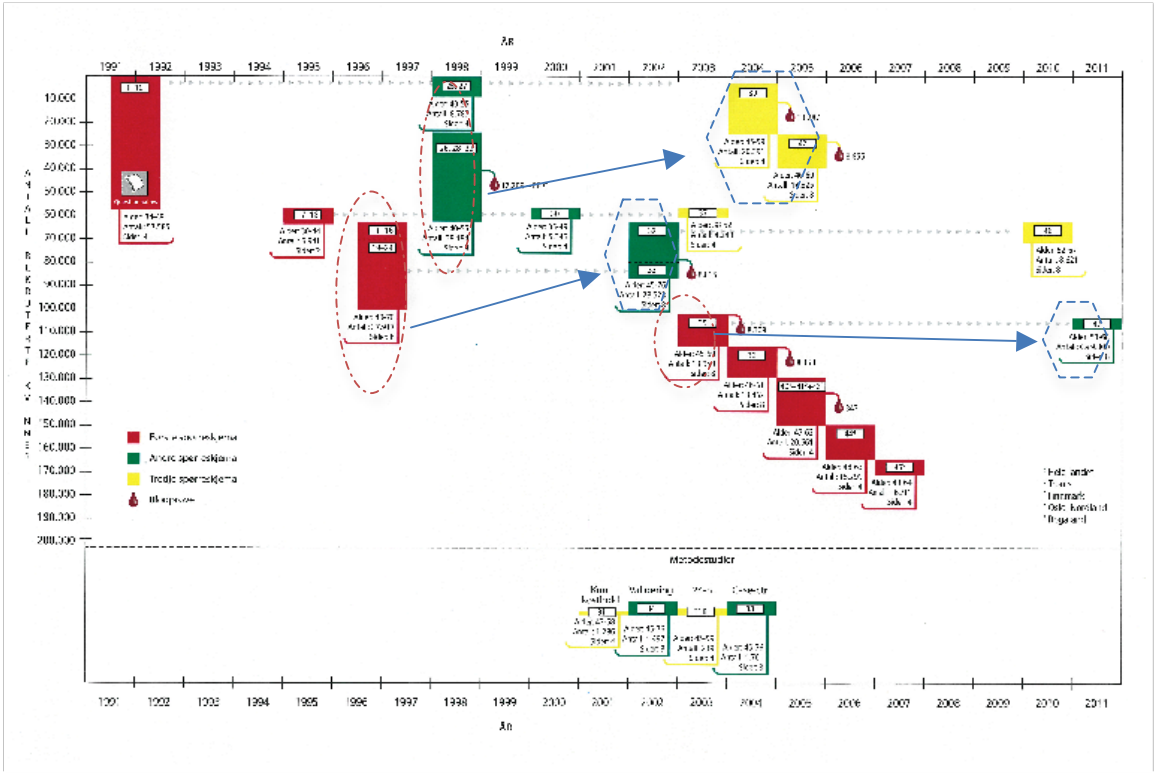


Figure 3-1Enrolment in the NOWAC study: adopted from Lund et al, 2008(40)

179,387 women aged 30-70 were invited in the NOWAC baseline and 102,540 of them were recruited during the year of 1991-1997. 80,693 women completed the second

mailing (response rate: 81%) over the years of 1998-2002 and 49,111 women completed the third mailing over the years of 2004-2005. In addition during the years of 2003-2004, 60,000 women aged 45-60 and during the years of 2005-2006 other 60,000 women of the same age were invited through Statistics Norway to extend the cohort. See Figure 3-2

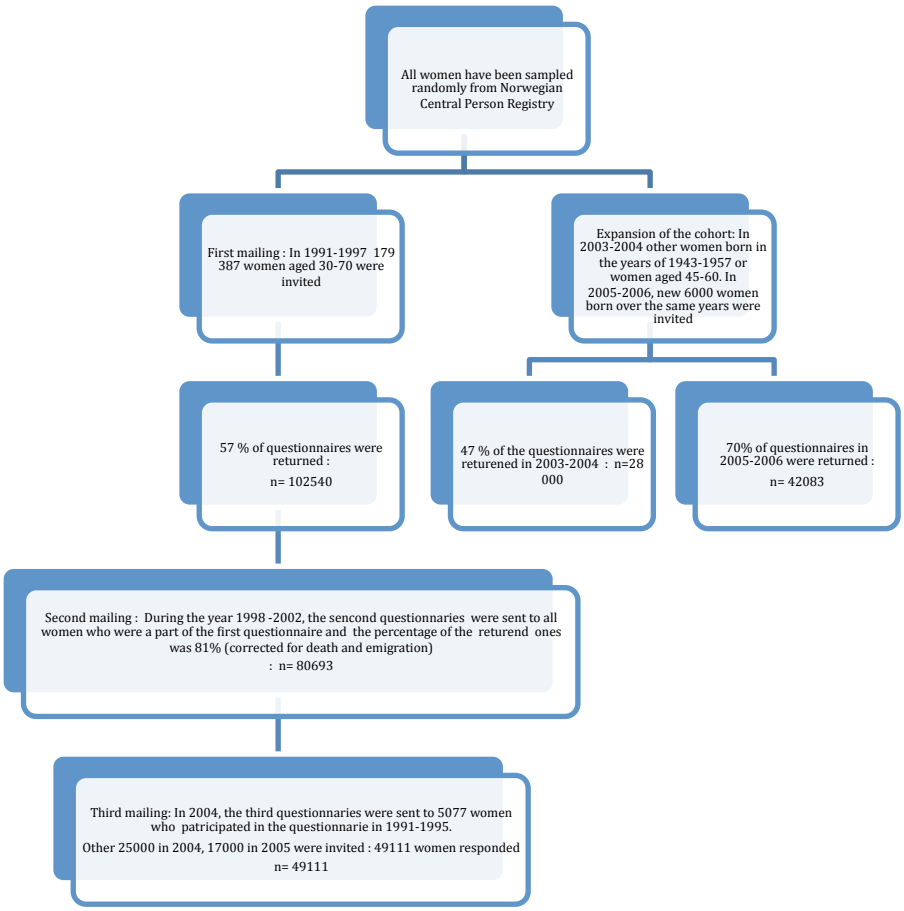


Figure 3-2 Participants, questionnaires and follow-up

3.2 Ethical consideration

This research utilized data from NOWAC study, which was approved by the Regional Committee for Medical and Health Research Ethics (REK) and the National Data Inspectorate from the Norwegian Directorate for Health. The existing approvals cover this

research study; hence there was no need to seek for a new approval for this study. The participants also gave their informed consent for the study. The use of data file was granted by Data & Publication Committee of the Department of community medicine of UiT-The Arctic University of Norway.

3.3 Study cohort: Inclusion & Exclusion criteria

The participants in three separate study periods who participated in both the first and second enrollments of NOWAC cohort were selected as the baseline study population for this thesis: the participants recruited in 1996- 1997(age: 40-70), 1998 (age: 40-55), and 2003(age: 45-60). Participants in other recruitment periods were not included in the study due to the lack of required dietary data. The criteria of the inclusion criteria in the study population are below. Only participants with complete dietary data both at the chosen baseline of the study and at the end of follow-up were included in analysis. Figure 3-3 shows the series in the baseline of thesis and thesis follow-up. Those participants who reported myocardial infarction (heart attack) at the study baseline were excluded.

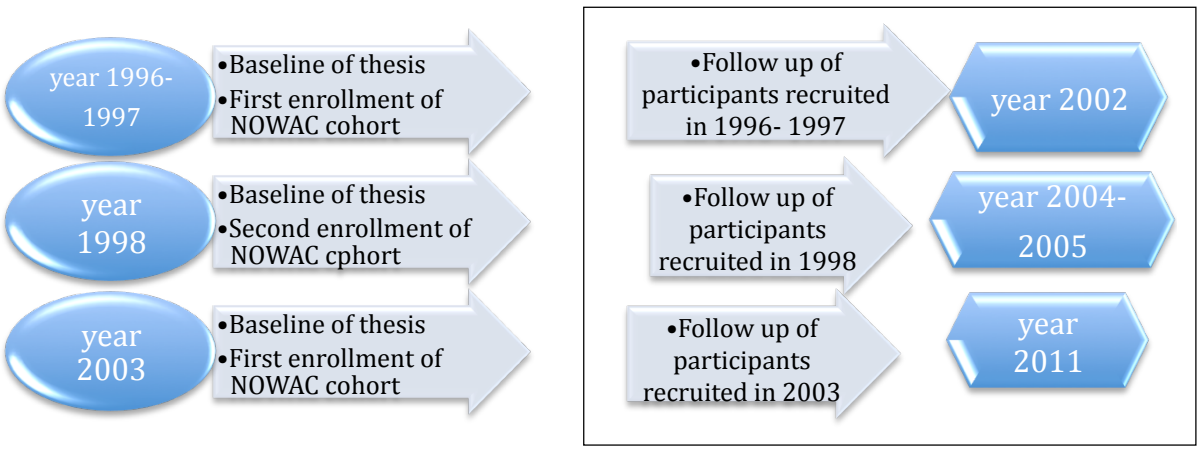


Figure 3-3Baseline of the study and the end of follow-up in 2002,2004-2005 and 2011

3.4 Information on the main Covariates

We included four covariates in the analysis, and these are, age, smoking status, physical activity, and the body mass index (BMI).

Smoking status is categorized into 3 different groups: never, ex-smoker and current smoker. The level of physical activity was categorized into four different groups by physical activity score (1: minimum, 10: maximum): inactive (1-3), moderately inactive (4-5), moderately active (6-7) and active (8-10). The BMI is the body weight in kilograms divided by height squared in meters. BMI were categorized into four groups: Underweight (BMI <20 kg/m2), normal weight (BMI 20 to 25 kg/m2), overweight (BMI 25 to 30 kg/m2) and obese (BMI >30 kg/m2).

3.5 Missing data

Missing data in the food frequencies questionnaires were treated as null intake, and missing data in the food portion were computed as the smallest portion size (45).

3.6 Exposure information

Intake of saturated fat is calculated as grams per day from FFQ. Intake of saturated fat is categorized into groups (quartiles) to check for the relationship between fat intake and the risk of myocardial infarction.

3.7 Outcome assessment

The outcome in the analysis shall be self-reported myocardial infarction in the follow up questionnaires from the second or third mailings.

3.8 Follow up, Censoring and Endpoints

Figure 3-2 and 3-3 shows thesis baseline enrolled participants at 1996-1997, 1998 and 2003 and they were followed up after 5-7years. Participants were followed up through the national registry of Norway by the use of their 11-digit personal identification numbers to identify deaths, emigrations and the first myocardial infarction. The endpoints were year 2002, 2005 and 2011, respectively. Person years will be calculated from the start of follow up to the date of the first myocardial infarction. Emigrations and deaths are reasons for censoring.

3.9 Statistical analysis

Statistical analyses were performed with the use of SPSS for Mac, version 22. The association between fat intake and incidence of myocardial infarction was evaluated by Cox proportional hazard model. Log (-log) plot and plotted Schoenfeld residuals were performed to test the assumption of proportional hazard.

4 RESULTS

4.1 The daily fatty acid intake and nonfatal myocardial infarction

Eligible study population was 60,203 Norwegian women with mean age of 51.17 years and the range between 41-70 years old. We excluded 377 subjects with history of previous MI at the time they were invited to the study. Thus 59,826 women without MI were used for the current analysis. During the 366214.4 person years of follow-up period (average follow-up period: 6.12 year), a total of 528cases of non-fatal myocardial infarction were identified. The crude incidence rate of non-fatal myocardial infarction was 144 per 100 000 person years. The overall mean SFAs intake was 25.38gram/ day (standard deviation, 9.64) and the average dietary intake (E %) of SFA was 13.34E% (standard deviation, 2.60).

Table 4-1 The NOWAC study: baseline characteristic of the study population

Study population	59826
Mean follow-up period in years (range)	6.12(4.33-9.65)
Person-years of follow-up	366214.36
Total non-fatal MI incidence	528
Percentage of population with non-fatal MI	0.9
Crude incidence rate (per 100,000 person-years)	144
Mean age in years(SD)	51.17(6.44)
Mean SFA in gram/day	23.58(9.64)
Mean SFA in gram/day of people with no MI	25.64(9.55)
Mean SFA in gram/day of people with MI	24.31(10.48)
Difference in gram/day between mean SFA for MI and no MI (p-value)	1.33(P<0.05)

The dietary advice from the Norwegian Directorate of Health's recommends that the intake of total fat range is 25% to 40% of energy intake, and whole saturated fats should not exceed more than 10% of energy intake. In the study population, the average dietary intake of total fat was 33.17E% while the mean of SFA was 13.34E% (Table 4-3). The proportion of SFA intake of energy intake among study subjects was above the recommendation

level. The Mean SFA of women who had MI during the follow-up period was 24.31gram/day (standard deviation, 10.48) and those who had not had MI was 25.64 gram/day (standard deviation, 9.55). Thus the difference in mean SFA between those who MI and those who does not MI was 1.13 and the p value of the difference was 0.04 which was less than 0.05(Table 4-1).

The mean daily monounsaturated fatty acids (MUFAs) intake was 19.46 gram (standard deviation, 6.86) and the mean of polyunsaturated fatty acids (PUFAs) intake was 11.45 gram/day (standard deviation, 4.84). The mean of trans fatty acids (TFAs) was 1.26 gram (standard deviation, 0.54).

Figure 4-1 The mean percentage of energy from protein, fat and carbohydrates in NOWAC study

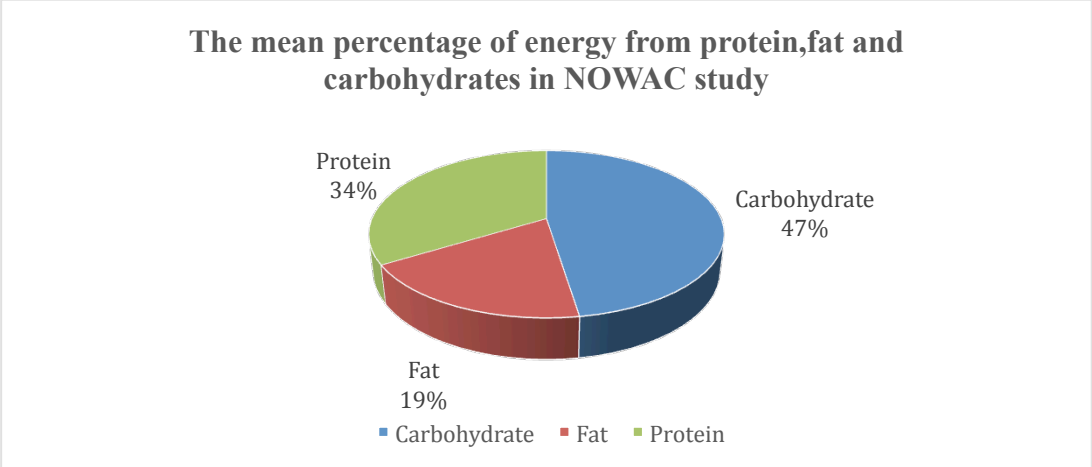


Table 4-2 The percentage of energy from dietary fatty acids in NOWAC study

	The mean percentage of energy from dietary in NOWAC study	Recommended percentage of energy from dietary in Norway
Total fat	33.17E% (SD 5.19)	25-40E%
SFA	13.34E% (SD 2.60)	<10E%
MUFA	10.30E% (SD 1.94)	10-20E%
PUFA	6.04E% (SD 1.68)	5-10E%
TFA	0.66E% (SD 0.18)	<1E%

4.2 Baseline characteristics according to SFA intake quartiles

At baseline (table 4-1), the overall mean SFA intake was 25.38gram/ day. We divided the saturated fat intake into four equal groups by rank. 1st quartile (Q1= 25th percentile) was the lowest 25% of saturated fat intake. 2nd quartile (Q2= 50th percentile) is until the median and the last cut point is Q3 (=75th percentile). The proportion of obese (BMI 25-25.99)/ overweigh (BMI≧ 30) increased in lower SFA intake group, and the women with highest SFA consumption group (4th quartile SFA) smoked currently more than 1st ,2nd, and 3rd SFA intake quartile groups. The non-fatal MI incidence occurred highest among 1st SFA quartile group. The percentage of the women with MI incidence was 1.10% in the 1st SFA intake quartile group and in the 2nd, 3rd and 4th quartile groups' incidence of MI was 0.8%.

Table 4-3 Baseline characteristics of the study populations according to SFA intake percentile group

	SFA intake (gram/day)			
	1st quartile:SFA ≦ 19	2nd quartile:SFA 19-24	3rd quartile:SFA 24-30	4th quartile **SFA≧** 30
Women (n=59826)	14897	14953	14975	15001
Mean age in years (SD)	52.27(6.67)	51.30(6.39)	50.69(6.22)	50.43(6.33)
Number of MI identified (%)	170 (1.1%)	118(0.8%)	127(0.8%)	114(0.8%)
Smoking status (%)				
Never	36.4	38.7	39.5	39.2
Former	34.0	33.6	31.8	28.0
Current	27.3	26.2	27.0	31.2
Missing	2.3	1.5	1.6	1.6
Body Mass index (%)				
BMI ≦ 20	5.6	6.6	7.4	11.8
BMI 20.01-24.99	45.5	48.9	51.2	52.1
BMI 25-29.99	35.3	33.4	31.5	26.9
BMI≧ 30	10.8	9.5	8.1	7.7
Missing	2.7	1.6	1.7	1.4
Physical activity (min=1 to max=10) (%)				
Inactive (1-3)	12.7	11.7	10.5	10.7
Moderately inactive (4-5)	34.2	36.4	37.5	33.9
Moderately active (6-7)	28.4	32.1	32.7	33.3
Active (8-10)	12.0	12.3	12.9	15.6
Missing	12.7	7.4	6.3	6.4
The use of hypertensive medicine				
Never	62.9	64.2	66.9	69.0
Former	10.6	9.9	9.2	8.7
Current	22.9	22.7	21.2	19.5
Missing	3.6	3.2	2.7	2.9

4.3 Relationship between the intake of SFAs and the incidence of non-fatal myocardial infarction (MI)

The outcome of this study was defined as non- fatal MI during the follow-up period (the average follow-up period is 6.12 years). During the follow up, 528 participants had first non-fatal myocardial infarction (rate of 144 per 100 000 person-years at risk). The relative risk of nonfatal MI associated with SFA intake quartile at baseline were estimated through the Cox proportional hazard model, with highest SFA intake group which is 4th quartile (SFA intake ≧ 30) as the reference and potential confounding factors, like age at baseline, smoking status, physical activity, BMI categories and the use of hypertensive medicine. To describe the relative risk of nonfatal MI according to SFA consumption, hazard ratios (HR) and their 95% confidence intervals (95%CI) was used.

Unadjusted and adjusted HRs for occurrence of non-fatal MI according to SFA intake categories are presented (table 4-4). The figure 4-2 depicts the time to myocardial infarction by saturated fat intake quartile categories.

In the unadjusted analysis, the HRs for MI tended to increase by lower SFA quartile. The relative risk for myocardial infarction was highest in the 1st quartile SFA intake group that is lowest SFA consumption group. Experiencing the event of myocardial infarction in the 1st quartile SFA intake group was 76 % (95% confidence interval=1.39- 2.24) higher hazard than the reference group (the 4th quartile SFA intake) without adjustment.

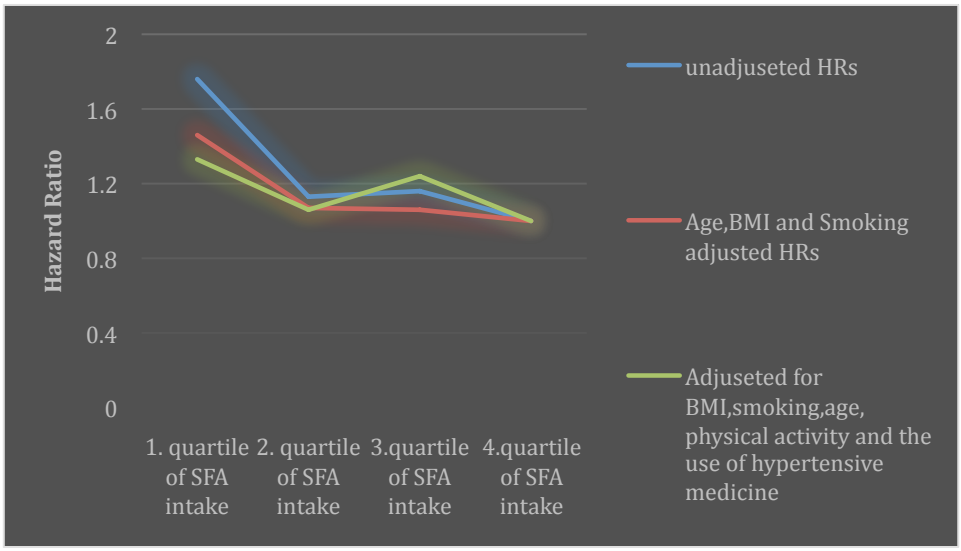
After adjusting age, smoking and BMI, the 1st quartile SFA intake group has 46% higher hazard than the reference group with 95% confidence interval (CI=1.14-1.86) while after

adjusting for age, smoking, BMI, physical activity and the use of hypertensive medicine, the 1st quartile of SFA intake group had the highest risk of MI occurrence (HR =1.33, 95% CI= 1.02-1.74). We then stratified according to BMI categories (Table 4-5), a decreased in the risk of MI was found in the lowest SFA intake category among the underweight (BMI ≦ 20) women group (BMI ≦ 20: HR=0.64, 95% CI= 0.21-1.98) when compared to the reference group. This tendency was same in the 3rd quartile SFA intake category (BMI ≦ 20: HR=0.68, 95% CI = 0.26-1.75). An increased risk tendency of MI was still found in the lowest SFA intake group among normal (BMI 20.01-24.99: HR=1.50, 95% CI=0.99-2.26), overweight (BMI 25-29.99: HR=1.54, 95% CI=0.99-2.41) and obese (BMI≧ 30: HR=1.10, 95% CI=0.53-2.29) groups. However it was not significant. Our primary objective was to assess the relationship between the intake of SFAs and time to first time nonfatal MI. Our results show that there may no association between SFA intake and non-fatal MI incidence.

Table 4-4 Relationship between SFA intake and non-fatal MI incidence with Hazard ratios (95% confidence interval)

	SFA intake (gram/day)				
	1.Quartile:SFA ≦ 19	2.Quartile:SFA 19-24	3.Quartile:SFA 24-30	4.Quartile **SFA**≧ 30	Total
Population (n=59826)	14897	14953	14975	15001	59826
Person-years of follow-up	90139.29	91362.22	92003.17	92709.68	366214.36
Number of MI identified (%)	170 (1.1%)	118(0.8%)	127(0.8%)	114(0.8%)	528(0.9)
Crude IR·	189	129	137	123	144
Unadjusted Hazard ratio	**1.76**	1.13	1.16	1.00	
(95% confidence interval)	**(1.39-2.24)**	(0.97-1.46)	(0.90-1.49)	(Reference)	
Hazard ratio adjusted for age, smoking and BMI	**1.46**	1.07	1.19	1.00	
(95% confidence interval)	**(1.14-1.86)**	(0.82-1.40)	(0.92-1.54)	(Reference)	
Hazard ratio adjusted for potential confounding factors[1]	**1.33**	1.06	1.24	1.00	
(95% confidence interval)	**(1.02-1.74)**	(0.80-1.40)	(0.92-1.58)	(Reference)	

Figure 4-2 Hazard ratios of non-fatal MI incidence according to SFA intake categories



· Crude IR = crude incidence rate per 100,000 person year

[1] Adjusted for age at baseline, smoking status, BMI, physical activity and the use of hypertensive medicine

Table 4-5 HR[2]s of MI incidence according to SFA intake and BMI

		SFA intake (gram/day)			
		1.Quartile:SFA ≦ 19	2.Quartile:SFA 19-24	3.Quartile:SFA 24-30	4.Quartile **SFA**≧ 30
Population (n=59826)		14897	14953	14975	15001
Total non fatal MI incidence (n=528)		170	118	127	114
Body Mass index (%)					
BMI ≦ 20	HR(95% CI)	0.64 (0.21-1.98)	**0.11(0.01-0.82)**	0.68(0.26-1.75)	1.00(reference)
BMI 20.01-24.99	HR(95% CI)	1.50(0.99-2.26)	1.38(0.91-2.09)	1.22(0.79-1.87)	1.00(reference)
BMI 25-29.99	HR(95% CI)	1.54(0.99-2.41)	1.08(0.67-1.76)	1.25(0.77-2.01)	1.00(reference)
BMI≧ 30	HR(95% CI)	1.10(0.53-2.29)	0.91(0.42-1.97)	1.64(0.82-3.28)	1.00(reference)

[2] Adjusted for age, smoking, physical activity, and the use of hypertensive medicine

5 Discussion

5.1 Discussion of the main findings

This study found no significant association between the consumption of saturated fat and the risk of myocardial infarction. Thus, the hypothesis that higher saturated fat intake in diet increase the risk of myocardial infraction was rejected. After adjusting for age, smoking, BMI, physical activity and the use of hypertensive medicine, 1st quartile group of SFAs has 33% higher hazard than the reference group (4th quartile group: highest SFA consumption group) with 95% confidence interval (CI=1.02-1.74). Lowest saturated fat intake group showed increased risk of MI compared to highest saturated fat intake group. When we stratified according to BMI categories, however, a lowest SFA consumption did not appear to affect the risk of non-fatal MI occurrence (Table 4-4 and 4-5).

This finding is supported by a recent meta-analysis conducted by Siri-Tarino et al (2010). They conducted the meta-analysis of 21 prospective cohort studies to estimate the association of between dietary saturated fat intake and risk of cardiovascular disease. The result showed that there was no association of the saturated fat intake with increased risk of CVD/CHD(16). Studies conducted by Gibson et al (2009) and Chowdhury et al (2014) also have showed that there is no significant evidence that the SFA intake is associated with higher risk of CVD/CHD(14, 15).

On the contrary, some other studies have shown that reduced saturated fat intake was associated with a lower risk of Myocardial infarction(9, 46). The study of Hu et al (1997) conducted in the Nurses´ Health Study Cohort Study have revealed that a higher saturated

fat consumption was associated with increased risk of both non-fatal myocardial infarction and coronary heart disease mortality(46).

Our founding of no association with saturated fat intake with non-fatal myocardial infraction could, at least in part, be explained below factors. Firstly, it may be affected by biases in self-reported questionnaires, although FFQ in NOWAC study have good reproducibility of dietary intake(45, 47). Secondly, the important potential confounders (age, smoking status, BMI, physical activity and the use of hypertensive medication) are adjusted for in our analysis. However, the lack of information of lipid lowing medication could reflect the appearance of no association between dietary intake of saturated fat and the risk of MI occurrence. Thirdly, how FFQ deal with the missing data of could be influenced in our result in some degree. The missing value in FFQ was treated as null consumption so missing data was gathered into the 1st quartile of saturated fat intake.

The lipid hypothesis has led to the wide spread belief that myocardial infarction is caused by high saturated fat intake. Presently, however, there is an ongoing debate on the issue of whether or not saturated fat is a risk factor to the cardiovascular disease (14). The issue of replacing saturated fat with either unsaturated fat or carbohydrate may be important. Some argue that if reduced saturated fat is replaced with carbohydrate, there may be more ill effects on health, such as obesity and diabetes, and no effect on reducing the risk of heart disease (48-50). Further studies should assess how the relationship between the saturated fat reduction and replacement by other macronutrient influence the risk of cardiovascular disease.

Our finding may indicate that a high dietary SFA intake may not the risk factor of myocardial infarction. Current recommendations for dietary saturated fat intake take this

founding into consideration because our finding does not support the current recommendation.

5.2 Methodological considerations

This study sought to investigate the association between the saturated fat intake and the risk of non-fatal myocardial infarction by analyzing data from a prospective cohort study. The study population was randomly invited through the national identification number and the overall response rate to the FFQ in the NOWAC study was around 50-80% which is relatively high. At enrollment, the outcome of interest has not occurred. Thus, there is no selection bias by the outcome.

There are potential problems with self-reporting questionnaires due to recall bias and social desirability bias. In epidemiological study, the measurement of exposure and outcome should be measured as accurately as possible to diminish systematic error. Measurement error leads to information bias. Thus, validity and reliability of the instrument to measure dietary intake, disease outcome and other characteristics of interest should be assessed.

5.3 Validity and reliability of FFQ

Information bias is related to the accuracy of measurement by FFQ and can affect the estimated risk of outcome variable. Participant record their average consumption of food item over past year through choosing from four to seven frequency choices (e.g. never/seldom, 1-3 times per month, once per week, twice per week, 3 times per week, 4-5 times per week, 6-7 times per week), frequency of certain amount or in natural unit and

standard portion size. The food frequency record was computed to daily intakes of food, energy and nutrients(51). Does NOWAC FFQ measure what we want to measure? Does it bring consistent result when we apply them another time? The prospective NOWAC study has performed several methodological studies to assess the validity and reproducibility of their data collection instrument, FFQ, to avoid measurement error. The reproducibility study was conducted by random sub sample (n= 2000) of NOWAC cohort study in 2002 (n =14817). They received same questionnaire twice within three months to evaluate test- retest reproducibility of a FFQ. The result demonstrated that the reliability coefficients for food group and nutrients ranged from 0.5-0.7 and reproducibility are reported for similar instruments. However, there were indications of reporting bias for some seasonal food item. (51).

Within NOWAC study, the 24hours dietary recalls (24HDRs) were also used to assess diet and validity of the FFQ to avoid measurement error. 500 women were randomly selected from among those who had answered an FFQ for the 24 HDRs assessment. 238 completed four telephone interviews that was performed once every season to cover seasonal variation during a year. In the 24HDRs, trained interviewers asked these 238 participants to describe food consumption during previous day. In the comparison between FFQ and 24 HDRs, FFQ underestimated the intake of energy, fat, added sugar and alcohol compared to 24HDRs, but FFQ has strong ranking ability for foods eaten frequently and for macronutrients (47).

5.4 Confounding factors

Whereas health authorities recommended reducing saturated fat intake to decrease the risk of cardiovascular disease in population, the result of this thesis shows no consistent increase in the risk and even opposite in the 25th percentile group of saturated fat intake.

As discussed earlier, the NOWAC study is a national population based prospective study with large sample size and sufficient length of follow up time. Through the process of optimal study design, the study population can be said to be a representative of the NOWAC cohort. The problematic issues of bias due to self-reported questionnaires in NOWAC study were discussed above. In addition, statistical analysis was taken into consideration for important confounding factors. However, there is no information of lipid lowering medication. Lipid lowering medications are the most important cofounding factors because the high intake of saturated fat increased serum cholesterol level and the increased serum cholesterol level affect the risk of myocardial infarction. If the estimate of a measure of association between the saturated fat and the risk of myocardial infarction were distorted by the lipid lowing drugs (LLDs), LLDs are confounding factor in this thesis. Then participants who are already using lipid lowing medication at the baseline need to be considered as the list of exclusions in the study population.

LLDs sales have been increased from 1994 in Norway. (52) The participants for the baseline of this study were recruited in 1996- 1997(age: 40-70), 1998 (age: 40-55) and 2003(age: 45-60) which were period of steady increasing of LLDs use in Norway.

6 Conclusion and recommendations for future research

This study suggests that there is no association between saturated fat intake and the risk of non-fatal myocardial infarction. However, there is a possibility that this result might have been influenced by the effect of confounding factors in some degree. This thesis provides recommendations for future research. The NOWAC study is national based prospective cohort study and follows up cohort to investigate natural history of disease or risk factors. However, in the NOWAC study, information on patients on lipid lowering medicine was not collected. Further study is therefore needed to verify the effect of possible lipid lowering medicine that participants in the NOWAC study might be placed on. It would be worthwhile to therefore ask for permission to access medical records of participants in the NOWAC study to investigate this. Another possibility is sending out questionnaires to the participants specifically requesting information on use of lipid lowering medicines as well as duration of use thereof. This information would be quite significant in understanding the relation between fat intake and the risk of coronary heart disease.

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Appendices 1

English translation of the questionnaire from series 39

WOMEN AND CANCER Confidential Autumn 2004
If you agree to take part, tick YES in the box to the right.
If you do not wish to take part, avoid reminders by ticking NO and return the questionnaire in the envelope provided.
We ask you to fill out the questionnaire as accurately as possible.
The questionnaire is to be read optically. Please use blue or black pen. Use of comma is not allowed, round up from 0.5 to 1. Use block letters.
Best wishes,
Eiliv Lund Professor dr. med.

Menopause

Do you still have regular periods?
... Yes
... Have irregular periods
... Unknown (Absent because of illness, etc.)
... Unknown (Current use of medication containing estrogen) ... No
If No;
Age when periods stopped? .....years

Pregnancies, births and breastfeeding

Have you ever been pregnant? Yes/No
If Yes; how many children have you born totally? .....children How old were you at last birth? .....years

Use of contraceptive pill

Have you ever used the pill or minipill Yes/No
If Yes; In how many years have you used the pill totally? .....years Are you currently on the pill? Yes/No

Use of hormone preparations with estrogen in menopause

Have you ever used estrogen pills/plasters? Yes/No
If Yes; how long have you used estrogen pills/plasters in all? .....years How old were you when you first used estrogen pills/plasters? .....years Are you currently using pills/plasters? Yes/No
Have they stopped of their own accord? .....
Have both your fallopian tubes been removed?... Have you had your womb removed (hysterectomy)?... Other? ...
If you replied “Yes”, we ask you to elaborate further on this by answering the questions below. For each period of continuous use of the same estrogen preparation, we hope you can tell us how old you were when you started, how long you used the same hormone preparation, and what it was called. If you stopped using it for a while, or switched to other preparations, you should count this as a new period. If you cannot remember the name of the hormone preparation, write 'Unsure'. To help you remember the names of estrogen preparations, please use the brochure provided, which contains pictures of estrogen preparations that have been sold in Norway. Please also give the number of the estrogen pill/plaster given in the brochure.
I agree to take part in
YES
the questionnaire survey NO

Age at start	Used same estrogen pill/plaster continuously from 1998			Name of estrogen pill/plaster (see brouchure)
	Year	Month	Nr	
1.				
2.				
3.				
4.				
5.				

Estrogen preparations for vaginal use

Have you ever used estrogen creams/suppositories? Yes/No
If Yes; Are you currently using creams/suppositories? Yes/No

Intrauterine device

Have you ever used an intrauterine device (Levonova)? Yes/No
If Yes; for how long have you used an IUD all together? ..... years How old were you the first time you got an IUD inserted? ..... years Are you currently using an IUD? Yes/No

Self-perceived health

Do you rate your own current state of health as (tick one box only): ... Very good ...Good ...Poor ... Very poor

Illness

Do you have or have you had any of the following illnesses? (tick one or more boxes)
Yes/ No - If Yes, age when first discovered
Cancer
High blood pressure
Heart failure/heart cramps Heart attack
Stroke
Diabetes
Depression (seen a doctor) Hypothyreosis
For the following conditions, tick which year they emerged, or give the year for the period before 1991.
Muscle pains (myalgia) Fibromyalgia/fibrositis Chronical fatigue syndrome Backpains of unknown cause
Whiplash
Osteoporosis
Fractures
Forearm (wrist)
Spine (compression)
Other fractures, describe.....

Other medication

Do you currently use any of these preparations daily? Yes/No Fontex, Fluoxetin
Cipramil, Citalopram, Desital
Seroxat, Paroxetin
Zoloft
Fevarin
Cipralex
before 98
98 99 00 01
02 03
If Yes; for how long time have you used this preparation continuously? Months..... Years..... Have you ever used any of these preparations? Yes/No
If Yes; For how long time did you use these preparations continuously? Months..... Years.....

Height and weight

How tall are you? .....cm
How much do you weigh at the moment? .....kg
What was your weight at age 18? .....kg
Body type 1.st degree (tick one box only):
....Very thin .... Thin ....Normal ....Heavy ....Very heavy

Smoking habits

During life, have you smoked more than 100 cigarettes totally? Yes/No
If yes, please fill in how many cigarettes you smoked on average per day the last five years. Number of cigarettes smoked per day
0 1-4 5-9 10-14 15-19 20-24 25+ How old were you when you smoked your first cigarette? ..... years Do you smoke on a daily basis at the moment? Yes/No
If No, how old were you when you quit? ..... years Did any of your parents smoke when you were child? Yes/No
If Yes, how many cigarettes did they smoke in total per day? .... cigarettes Breast cancer in the family
Have any of your close relatives had breast cancer:
Yes No Unknown Age at start
Daughter Mother Sister

Mammography screening

Have you ever been to mammography screening of your breasts? Yes/No
If Yes; How old were you first time? ..... years How many times have you been screened?

- - After invitation from the Mammography Programme ..... times
- - After referral from doctor ..... times
- - Without referral from doctor ..... times

Physical activity

Please indicate the level of your physical activity on a scale from very low to very high by age 14, 30 and today. The scale goes from 1-10. By physical activity we mean both work in and outside the home, as well as training/exercise and other physical activity, such as walking, etc.

Age Very low Very high
14years 1 2 3 4 5 6 7 8 9 10 30years 1 2 3 4 5 6 7 8 9 10 Today 1 2 3 4 5 6 7 8 9 10
How many hours per day do you walk or stroll ourdoors at mean?
Winter Spring Summer Autumn
Seldom/ Less than 1⁄2-1 Never 1⁄2 hour hour
1-2 more than hours 2 hours
How many stairs (whole floors) do you walk per day on average? .....
For each of the following activities you partake in, we ask you to estimate how many minutes per day you use on these activities on average.

Minutes

Activity Winter Spring Summer Fall
Watch TV Reading Handicraft
Gardening Shower/bath/ personal care Exercise/jogging Bicycling
How many hours per day on the workplace do you on average use to
Sit..... Stand.....
Walk..... Lift..... Heavy lifting/caretaking.....
Hours

Diet

Do any of the following affect your diet? (More than one tick allowed)
Vegetarian... Do not eat Norwegian diet on daily basis... Have allergy/intolerance... Chronic illness... Anorexia... Bulimia... Try to lose weight... Low GI food...
We are interested in finding out about your usual eating habits. For each question, tick how often in the last twelve months you have eaten the food in question, and how much you usually eat/drink each time.

Drink

How many glasses of each kind of milk do you usually drink? (Tick one box on each line).
Full cream milk (sweet, sour) Semi-skimmed milk (sweet, sour) Extra skimmed milk
Skimmed milk (sweet, sour)
Boiled coffee (kokekaffe) Filter coffee
Instant coffee
Black tea
Green tea
Orange juice
Lemonade/soft drinks with sugar Lemonade/soft drinks with sugar Sugarfree lemonade/soft drinks
Never/ 1-4 seldom wk
5-6/ 1/ wk day
2-3/ 4+/ day day
How many cups of each kind of coffee/tea do you usually drink? (Tick one box on each line)
Never/ 1-6 seldom wk
1/ 2-3/ day day
Tea Yes/No Yes/No
1/ 2-3/ day day
4-5/ 6-7/ 8+/ day day day
Do you use the following in coffee or tea:
Coffee Sugar (non-artificial sweetener) Yes/No Milk or cream Yes/No
How many glasses of water do you usually drink?
Never/ 1-6 seldom wk
Tap water and bottled water

How many glasses of juice, limonade and soft drinks do you usually drink? (Tick one box on each line)
Never/ 1-4 seldom wk
5-6/ 1/ 2-3/ 4+/ wk day day day

Yoghurt/cereals

How often do you eat yoghurt (equivalent to 1 carton)? (Tick one box only) .....never/seldom ....1/wk .....2-3/wk ....4+/wk
4-5/ 6-7/ 8+/ day day day
How often do you eat cereals, oat flakes or muesli? (Tick one box only) .....never/seldom .....1-3/wk .....4-6/wk 1/day

Bread

How many slices of bread/rolls and crispbread do you normally eat? (1/2 roll = 1 slice of bread) (Tick one box on each line)
Wholemeal bread Kneippbrød (semi white) White bread
Crispbread, etc.
Never/ 1-4 seldom wk
5-7/ 2-3/ wk day
4-5/ 6+ day day
Below are some questions on use of various kinds of sandwich filling/spread. We want to know how many slices of bread with these fillings/spreads you usually eat. If you also use these products on other things than bread (e.g., on waffles, in breakfast cereals, porridge), please take this into account when answering the questions.
How many slices of bread do you eat with? (Tick one box on each line)
Jam
Brown cheese, full cream Brown cheese, low-fat
White cheese, full cream
White cheese, low-fat
Meat fillings/spreads, liver paté Shrimp salad, Italian salad, etc.
Never/ 1-3 seldom wk
4-6/ 1/ 2-3/ 4+/ wk day day day
How many slices of bread per week on average in the last twelve months have you eaten with? (Tick one box on each line)
Never/ 1/
seldom wk Mackerel in tomato sauce, smoked mackerel
Caviar
Herring/Anchovies
Salmon (cured and smoked) Other fish fillings/spreads
2-3/ 4-6/ 7-9/ 10+/ wk week week week
What kind of fat do you usually spread on your bread? (Tick more than one box if necessary) ..... I do not use fat on bread
..... butter
..... hard margarine (e.g., Per, Melange)
..... soft margarine (e.g., Soft)
..... margarine/butter mix (e.g., Bremykt) ..... Brelett
..... low-fat margarine (e.g., Soft light, Letta) .... Middle fat margarine (Olivero, Omega)
If you use fat on your bread, how thick a layer do you usually spread on it? (Tick one box only) .... very thin scraping (3g) ..... thin layer (5g)
..... well-covered (8g) .... thick layer (12g)

Fruits and vegetables

How often do you eat fruit? (Tick one box per line only) Never/ 1-3 1/
2-4/ 5-6/ 1/ 2+/ wk wk day day
Apples/pears Oranges, etc. Bananas Other fruit
seldom month wk
How often do you eat various kinds of vegetables? (Tick one box per line)
Carrots
Cabbage
Turnip Broccoli/cauliflower Mixed salad Tomatoes
Mixed vegetables (frozen) Onions
Other vegetables
Rice
Spaghetti, macaroni, noodles
Never/ 1-3 1/ seldom month wk

2/ 3/ wk wk
4-5/ 6-7/ wk wk
For the vegetables you eat, tick how much you eat each time. (Tick one box for each kind) - carrots ....1/2 .....1 .....1 1/2 .....2+
- cabbage .....1/2dl .....1dl .....11/2dl .....2+dl
- turnip .....1/2dl .....1dl .....11/2dl .....2+dl
-broccoli/cauliflower .....1-2 rosette(s) .....3-4 rosettes .....5+ rosettes - mixed salad .....1dl .....2dl .....3dl .....4+dl
- tomatoes ....1/4 ....1/2 ....1 ....2+
- mixed vegetables .....1/2dl .....1dl .....2dl .....3+dl
How many potatoes do you usually eat (boiled, fried, mashed)? (Tick one box) ..... I do not/I seldom eat potatoes ..... 1-4/wk .....5-6/wk ..... 1/day ..... 2/day ..... 3/day .....4+/day

Rice, spaghetti, porridge, soup

How often do you eat rice and spaghetti/macaroni? (Tick one box on each line)
Never/ 1/ 1/ 2/ seldom month wk wk
3+/ wk
2-6/ 1+/ wk day
3+/ wk
How often do you eat porridge? (Tick one box only)
Never/ 1/ 2-3/ 1/
seldom month month wk
Rice porridge
Other porridge (oatmeal, etc.)
How often do you eat soup? (Tick one box on each line)
Never/ 1/ 1/ 2/
seldom month wk wk
As main course
As appetizer/lunch/evening meal

Fish

We would like to know how often you eat fish. Please fill in answers to the questions on fish consumption as fully as possible. The availability of fish may vary throughout the year. Please indicate in which seasons you eat the different kinds of fish.
Cod, saithe, halibut, pollack Wolffish, flounder, redfish Salmon, trout
Mackerel
Herring
Other fish types
Never/ Same amount seldom all year
Winter Spring
Summer Fall
In the periods of the year when you eat fish, how often do you usually eat the following? (Tick one box per line)
Never/ 1/ 2-3/ 1/ 2+/
seldom month month wk wk
Boiled cod, saithe, halibut, pollack Fried cod, saithe, halibut, pollack Wolffish, flounder, redfish Salmon, trout
Mackerel Herring
Other fish types
If you eat fish, how much do you usually eat each time? (1slice/piece = 150g) (Tick one box on each line) - boiled fish (slice).....1 .....1.5 .....2 .....3+
- fried fish (piece).....1 .....1.5 .....2 .....3+
How many times per year do you eat fish feed? (Tick one box only per line) 0 1-3 4-6 7-9 10+
Roe
Fish liver
If you eat fish liver, how many tablespoonfuls do you usually take each time? (Tick one box only) .....1 .....2 .....3-4 .....5-6 .....7+
How often do you eat the following kinds of fish dish? (Tick one box only per line) Never/ 1/ 2-3/ 1/ 2+/
seldom month month wk wk
Fishcakes/pudding/balls
Fish stew, fish pie
Fried fish (in batter), fish fingers
How much do you usually eat of the various dishes? (Tick one box only on each line) Fishcakes/pudding/balls (pcs.) (2 fish balls = 1 fishcake).....1 .....2 .....3 .....4+ Fish stew, fish pie (dl).....1-2 .....3-4 .....5+
Fried fish (in batter), fish fingers (pcs.) .....1-2 .....3-4 .....5-6 .....7+

In addition to information regarding fish consumption, it is important to gather information on the accompaniments served with fish. How often do you use the following together with fish? (Tick one box per line only)
Melted or solid butter
Melted or solid margarine
Clotted cream (35%)
Reduced-fat cream (20%)
Sauce containing fat (white/brown) Non-fat sauce (white/brown)
Never/ 1/ seldom month
2-3/ 1/ 2+/ month wk wk
For the various kinds of accompaniments you eat with fish, please tick how much you would normally eat.
Melted or solid butter (tbs) .....1/2 .....1 .....2-3 .....4+ Melted or solid margarine (tbs) .....1/2 .....1 .....2-3 .....4+
Clotted cream (tbs) .....1/2 .....1 .....2-3 .....4+ Reduced-fat cream (tbs)....1/2 .....1 .....2-3 .....4+
Sauce containing fat (dl)...1/4 ....1/2.....3/4 .....1 .....2+ Non-fat sauce (dl) ....1/4 .....1/2 ....3/4....1 .....2+
How often do you eat shellfish (e.g., shrimp, crab)? (Tick one box only) ..... never/seldom ..... 1/mth ..... 2-3/mth .....1+/wk

Meat

How often do you eat reindeer meat?
... Never/seldom ...1/month ...2-3/month... 1 /wk ... 2-3/wk ... 4+/wk
How often do you usually eat the following meat and poultry dishes? (Tick only one box for each dish) Never/ 1/ 2-3/ 1/ 2+/
seldom month month wk wk
Steak (cow, pork, mutton) Chops
Beef
Meat balls, patties Sausages
Stews, hash
Pizza with meat Chicken
Bacon, pork Other meat dishes
If you eat the following dishes, how much do you usually eat? (Tick one box per line) Steak (slices) .....1 .....2 .....3 .....4 ... 5+
- Chops (pcs.) .....1/2 .....1 .....1.5 .....2+
- meat balls, - cakes (pcs.) .....1 .....2 .....3 .....4+
- sausages (pcs.a 150g) ....1/2 .....1 .....1.5 .....2+
- stew, hash (dl) .....1-2 .....3 .....4 .....5+
- pizza with meat (pcs a 100g) ....1 .....2 .....3 .....4+
Which sauces do you use to meat dishes and pasta dishes?
Gravy
Broth Tomato sauce Creamy sauce
How much do you usually eat of these sauces?
Gravy (dl) ...1/4 ...1/2 ...3/4 ...1 ...2+ Broth ...1/4 ...1/2 ...3/4 ...1 ...2+ Tomato sauce ...1/4 ...1/2 ...3/4 ...1 ...2+
Creamy sauce ...1/4 ...1/2 ...3/4 ...1 ...2+
Never/ 1/ seldom month
2-3/ 1/ month wk
2-6/ 1+/ wk day

Other types of food

How many eggs do you usually eat in the course of a week (fried, boiled, scrambled, omelette)?(Tick one box) .....0 .....1 .....2 .....3-4 .....5-6 .....7+
How often do you eat ice cream (for dessert, ice lollies, etc.)?
(Tick once to indicate how often you eat ice cream in summer, and once for the rest of the year)
Never/ 1/ 2-3/ 1/ 2-6/ 1+/ seldom month month wk wk day
- in summer
- rest of the year
How much ice cream do you normally eat each time? (Tick one box) .....1dl .....2dl .....3dl .....4+dl
How often do you eat sweet buns, cakes, Danish pastry, waffles, etc. (Tick one box)
Yeast baking (buns, etc.) Pastry(Danish, cream-filled) Cakes
Pancakes
Waffles
Biscuits, cookies
Lefser/lomper (Norwegian specialities)

Never/ 1-3/ 1/ seldom month wk
2-3/ 4-6/ 1+/ wk wk day
How often do you eat dessert? (Tick one box)
Never/ 1-3/
1/ wk
2-3/ 4-6/ 1+/ wk wk day
4-6/ 1+/ wk day
Pudding (chocolate, caramel) Ricecream ,mousse
Compote, fruit porridge, canned fruits Strawberries (fresh, frozen)
Other berries (fresh, frozen)
How often do you eat chocolate? (Tick one box)
Never/ 1-3/ 1/ 2-3/
seldom month wk wk
Dark chocolate Light chocolate
If you eat chocolate, how much do you usually eat each time?
Potato chips Peanuts Other nuts Other snacks
Cod liver oil and fish oil capsules Do you use cod liver oil (liquid)? Yes/No
If yes, how often do you use it?(Tick one box for each line) Never/ 1-3/ 1/ 2-6/
seldom month wk wk
- in the winter
- the rest of the year
How much cod liver oil do you usually take at one time?
.....1ts .....1/2ts .....1+ts
Do you use cod liver oil pills/capsules? Yes/No
seldom month
Use the size of a Kvikk-Lunsj (Kit-Kat) as a guide, and indicate how much you eat in relation to that) (Tick one box) .....1/4 .....1/2
.....3/4 .....1 .....1.5 .....2+
How often do you eat salty snacks? (Tick one box)
Never/ 1-3/ 1/ 2-3/
4-6/ 1+/ wk day
Daily
seldom month wk
wk
If yes, how often do you take cod liver oil pills/capsules? (Tick one box for each line) Never/ 1-3/ 1/ 2-6/ Daily
seldom month wk wk
- in the winter
- the rest of the year
Which type of cod liver oil pills/capsules do you usually use, and how many do you use to take each time?
Name.....Amount.....

Dietary supplements

Do you use other dietary supplements? Yes/No
If yes, how often do you take such supplements?
Never/ 1-3/ 1/ 2-6/ seldom month wk wk
Brand name:..... Brand name:..... Brand name:.....

Warm meals

How many times during a moth do you eat warm meals? ... Breakfast ...Dinner
... Lunch ... Evening meal
Daily

Alcohol

Are you a teetotaller? Yes/No
If No, how often and how much have you drunk on average in the last twelve months?
(Tick one box on each line)
Never/ 1/
seldom month
Beer (1/2l)
Wine (glass)
Spirits (shorts/cocktails) Liqeuers

Social conditions

Are you (tick one box only):
.....married ....cohabitant ....single...other ...divorced ...widow

How many persons are there in your household? Number: .....
What is your household's gross annual income?
.....less than 150 000 kr .....151 000-300 000 kr .....301 000-450 000 kr .....451 000-600 000 kr .....more than 750 000 kr
What is your work situation?
2-3/ 1/ month wk
2-4/ 5-6/ 1/ 2+/ wk wk day day
... work full time ... work part-time ...retired ... work at home ...education ...disabled ... rehabilitation ...unemployed
Do you work outdoors in your job? Yes/No
If Yes; how many hours per week? ...Summer ...Winter

Sun habits

Do you get freckles when you sunbathe? Yes/No
To study the effect of sunbathing on risk of melanoma, we ask you to give information about skin colour.
Tick on the colour that best matches your skin colour (without sunbathing). (coloured scale 1-10)
How many times per year have you been sunburnt to the extent that you skin has become irritated and blistered, and peeled afterwards? (One tick for each age-group) Age Never Max 1/ 2-3/ 4-5/ 6 or more/
year year year year
40-49 50+
How many weeks on average per year have you taken sunbathes in southern Europe?
Age Never 1 wk 2-3 wk 4-5 wk 7+wk 40-49
50+
The last 12 months
How often have you been sunbathing in solarium?
Age Never Seldom 1/month 2-3/month 3-4/month 1+/wk 40-49
50+
The last 12 months
How often do you shower or take a bath?
With soap/shampoo Without soap/shampoo
1+/ 1/ 4-6/ day day wk
2-3/ 1/ wk wk
2-3/ Seldom/ month never
When do you use cream with sun screen? (more than one tick possible)
....At Easter ....in Norway or outside southern Europe? ....sunbathing in southern Europe
Which sun factors do/did you use in these periods?
None 1-4 5-9 10-14 15+
Easter
Norway/outside south Europe South Europe
How many irregularly shaped moles larger than 5mm do you have in total on both legs (between the toes and the groin)? Three examples of moles larger than 5mm are shown below.
.....0 .....1 .....2-3 .....4-6 .....7-12 .....13-24 .....25+
How often do you use the following skin care products? (Tick one box)
Face cream Hand cream Body lotion Perfume
Never/ 1/ seldom month
2-3/ 1/ month wk
2-4/ 5-6/ 1/ 2+/ wk wk day day
Finally we would ask about your permission to contact you again per post. We will get your address from the central person registry. Yes/No
Are you willing to give a blood sample? Yes/No