Relation between blood lipid levels and diet and characterization of food choices in children with familial hypercholesterolemia

Master Thesis by

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Acknowledgements

This work has been conducted at the Department of Nutrition, University of Oslo and at the Lipid Clinic, Rikshospitalet, Oslo University Hospital

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Summary

Background and aims: Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated levels of low density lipoprotein (LDL) cholesterol and increased risk of premature cardiovascular disease (CVD). The treatment of FH involves lipid-lowering drug therapy and dietary counseling, the latter being the primary treatment in children. The observed lipid lowering- and CVD preventing effects of certain dietary patterns in the general population support the inclusion of dietary counseling in the treatment of FH. Still, the effects of lipid lowering dietary treatment in this disease are not clear. Possible different effects of maternal and paternal inheritance of FH are also a largely unexplored field. The aim of this thesis is to increase knowledge about the diet of children with FH, to compare their diet to that of other non-FH children, and to investigate the relation between a dietary score and blood lipids. In addition we wanted to explore whether paternal/maternal FH affect dietary score, blood lipids and C-reactive protein (CRP) differently.

Subjects and methods: The diet of 112 children and young FH subjects (of which 43 were between 11 - 15 years) and 29 children without FH (aged 13 years old) was investigated by use of the SmartDiet questionnaire. The SmartDiet scores and the use of different food items of the FH children aged 11-15 years old were compared to those of the children without FH. (The SmartDiet scores and the use of different food items among the entire group of FH subjects were also analyzed.) Blood lipid levels of the FH subjects were retrieved from their medical records at the Lipid Clinic, and blood lipid levels were obtained from the non-FH children. The relations between SmartDiet scores and lipid levels were analyzed. Lipid levels of FH subjects with maternal and paternal FH were compared, as were their SmartDiet scores.

Results: The FH children aged 11-15 years had significantly higher SmartDiet scores than the non-FH children. (The score of the subgroup of FH children was very similar to that of the entire FH group.) Both the FH subjects and the non-FH children could improve diet to make it healthier. Regarding the use of different foods, the FH children aged 11-15 differed from the non-FH children as significantly higher proportions of the FH children used low-fat products among types of milk, meat and cheese or products high in unsaturated fatty acids when choosing butter/margarine. No differences were observed regarding use of fruits/vegetables/berries, fish, grain products high and low in fiber or snacks. A significantly higher proportion of the FH children used sweet spreads/sweet drinks. No significant
correlations were observed between lipid levels and SmartDiet scores, except a moderate inverse correlation with triglycerides level among the non-FH children. SmartDiet scores of FH subjects with maternal FH did not differ from the SmartDiet scores of those with paternal FH. No significant differences in lipid levels or CRP were observed between FH subjects with maternal/paternal FH among those who were not statin treated. Among those who were statin treated, FH subjects with paternal FH had significantly lower apo B/apo A1 ratio than those with maternal FH.

**Conclusion:** Our results suggest that FH children have a healthier diet than non-FH children, and that the dietary treatment that they, and their parents, receive is effective in terms of promoting healthy food choices. However, there appears to be considerable room for improvement regarding healthiness and “heart-friendliness” of the diet of children and young FH subjects as well. We found no relationship between diet and blood lipids in FH children in this study. Larger, better controlled studies with more comprehensive dietary assessment methods should be conducted in order to investigate this further. Maternal/paternal FH does not seem to influence the healthiness of diet in children and young with FH differently. Whether inflammation and lipid levels differ between FH subjects with maternal/paternal FH needs to be further investigated.
# Table of contents

Acknowledgements .................................................................................................................. III
Summary ................................................................................................................................ IV
Abbreviations ....................................................................................................................... VIII
List of tables and figures ....................................................................................................... IX
List of appendices ................................................................................................................ XI

1 Introduction ....................................................................................................................... 1

1.1 Cardiovascular disease ............................................................................................... 1

1.1.1 Atherosclerosis ....................................................................................................... 1

1.1.2 Cholesterol as a CVD risk factor ........................................................................... 2

1.2 Diet and cardiovascular disease .................................................................................. 6

1.2.1 Relations between diet and cardiovascular disease .............................................. 6

1.2.2 Dietary patterns and prevention of CVD ............................................................... 6

1.3 Dietary assessment ....................................................................................................... 8

1.3.1 Recording methods ............................................................................................... 9

1.3.2 Recall methods ...................................................................................................... 9

1.4 Familial hypercholesterolemia .................................................................................... 10

1.4.1 The genetic basis of FH ....................................................................................... 11

1.4.2 Clinical features of FH ....................................................................................... 12

1.4.3 Influence of maternal or paternal heredity ......................................................... 14

1.4.4 Treatment of FH ................................................................................................ 15

2 Aims of the study ............................................................................................................. 20

2.1 Specific objectives of this thesis ................................................................................ 20

3 Subjects and Methods ....................................................................................................... 21

3.1 Recruitment of participants ....................................................................................... 21

3.1.1 FH subjects ........................................................................................................ 21

3.1.2 Non-FH children .................................................................................................. 23

3.1.3 FH children aged 11-15 years ........................................................................... 24

3.2 Materials ....................................................................................................................... 24

3.2.1 Collection of dietary data .................................................................................... 24

3.2.2 Procedure for registration of dietary data ......................................................... 26

3.2.3 Collection of clinical and biochemical characteristics ...................................... 27
Abbreviations

Apo A1  Apolipoprotein A1
Apo B  Apolipoprotein B
CHD  Coronary heart disease
CIMT  Carotid intima-media thickness
CRP  C-reactive protein
CVD  Cardiovascular disease
FH  Familial hypercholesterolemia
FH (11-15)  FH subjects aged 11 to 15 years
HDL  High density lipoprotein
HDL-C  High density lipoprotein cholesterol
HMG-CoA  3-hydroxy-3-methyl-glutaryl Co-enzyme A
IDL  Intermediate density lipoprotein
IMT  Intima-media thickness
LDL  Low density lipoprotein
LDL-C  Low density lipoprotein cholesterol
LDL-R  Low density lipoprotein receptor
Lp(a)  Lipoprotein a
NCEP  National Cholesterol Education Program
SES  Socioeconomic status
SFA  Saturated fatty acids
TG  Triglycerides
VLDL  Very low density lipoprotein
WHO  World Health Organization
List of tables and figures

**Table 1**  
Nutrient composition of the therapeutic lifestyle changes diet, adapted from the NCEP Adult Treatment Panel III

**Table 2**  
Characterization of all FH subjects, FH children (11-15) and non-FH children, with comparison of the FH children (11-15) and the non-FH children

**Table 3**  
Characteristics and comparison of FH subjects receiving/not receiving statin treatment

**Table 4**  
SmartDiet scores of the total FH group, FH children aged 11-15 and non-FH children, with comparison between FH children aged 11-15 years and non-FH children

**Table 5a/b**  
Frequency table showing which food items among categories of foods that are chosen most frequently in FH subjects and non-FH children, with comparison of FH subjects aged 11-15 years and non-FH children (13 years old)

**Table 6**  
Spearman's rank correlation coefficient between SmartDiet scores and lipid levels and CRP in FH subjects, FH subjects aged 11-15 years and non-FH children (13 years old)

**Table 7**  
Spearman's rank correlation coefficient between SmartDiet scores and lipid levels and CRP in FH-subjects who are statin treated and FH-subjects who are not statin treated

**Table 8**  
Comparison of the SmartDiet scores and the lipid values between children and young adults with maternal- and paternal FH

**Table 9**  
Comparison of the SmartDiet scores and the lipid values between children and young with maternal- and paternal FH that are not statin treated

**Table 10**  
Comparison of the SmartDiet scores and the lipid values between children and young with maternal- and paternal FH that are not statin treated
Figure 1. Characteristic clinical features of FH.

Figure 2. Flow chart showing inclusion and exclusion of FH subjects.
List of appendices

Appendix 1: Approval from the Regional Committee of Medical Ethics

Appendix 2: Information letter that was sent to the invited FH subjects

Appendix 3: Informed consent scheme that was sent to FH subjects

Appendix 4: The SmartDiet questionnaire

Appendix 5: A short form to identify medication, presence of chronic disease, history of hospitalization and possible presence of cardiovascular disease in the family, sent to invited FH subjects

Appendix 6: Informed consent scheme that was handed non-FH children
1 Introduction

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world[1]. CVDs are disorders of the heart and blood vessels, of which the most prevalent forms are coronary heart disease (CHD) and stroke [2], mainly caused by atherosclerosis [3]. In 2008, CVD accounted for 30 % of all global deaths. The World Health Organization (WHO) has stated that more people die annually from CVDs than from any other cause [4]. In Norway, CVD accounts for approximately 37% of all deaths nationally [5].

Scientific evidence suggests that the risk of coronary events is largely associated with the presence of different risk factors [6]. Risk factors may be classified as modifiable and non-modifiable. Examples of modifiable risk factors are elevated blood pressure, obesity, diabetes, elevated cholesterol, unhealthy diet, smoking and low physical activity [7]. Heredity or family history, advancing age, gender and ethnicity are examples of non-modifiable risk-factors [8-10].

1.1.1 Atherosclerosis

Atherosclerosis is a progressive inflammatory disease, characterized by the accumulation of lipids and fibrous elements in the arteries [3, 11]. It is the main pathological process leading to coronary heart disease, cerebral artery disease and peripheral artery disease. Most of the devastating or fatal consequences of atherosclerosis are seen in elderly or middle-aged men and women[1]. Still, large scale studies have revealed that the process of atherosclerosis formation begins in childhood and progress through adolescence and early adulthood [12, 13]. Usually, atherosclerosis stays asymptomatic for a long time [1].

The initiation and progression of atherosclerosis may be considered as a multistep inflammatory process in the artery walls [11, 14]. The lesions are typically seen as asymmetrical focal thickenings of the innermost layer of the artery, intima [11]. Advanced, complicated atherosclerotic lesions may intrude into the lumen and alter the flow of blood [14].
Different risk factors of CVD may initiate the inflammatory response in the endothelium [15]. When injured, the normal homeostatic properties of the endothelium become altered through compensatory responses which include increased adhesiveness towards leukocytes and platelets and altered permeability [14]. Subendothelial retention of apolipoprotein B (apo B) containing lipoproteins may be considered the key initiating process in atherogenesis, with extracellular subendothelial proteoglycans being the most important lipoprotein-retaining molecules. The lipoproteins that are retained become modified through oxidation and aggregation. The modification may elicit a biological response that develops into a maladaptive inflammatory response [16].

When lipoproteins are retained and modified, monocytes enter the subendothelium, differentiate into macrophages and ingest the modified lipoproteins. Eventually they become cholesterol loaded foam cells [16]. Scientific experiments performed on lipid extractions from human atherosclerotic lesions provide evidence that the lesions contain oxidized low density lipoprotein [17]. The injury induced makes the endothelium form vasoactive molecules, growth factors and cytokines. Over time, the inflammatory response stimulates migration and proliferation of smooth muscle cells that become intermixed with the inflammation area to make an intermediate lesion. If the inflammatory response fails in neutralizing the initiating offending agent, the process may persist [14].

Continued inflammation causes the presence of macrophages and lymphocytes to increase. Cycles of mononuclear cell and smooth muscle cell (SMC) recruitment enlarges the lesion. The SMC promote the formation of a fibrous cap, which covers the accumulated core of lipid and necrotic tissue [14]. As the lesion progresses, thinning, erosion or rupture of the fibrous cap may lead to the formation of a thrombus, potentially occluding an artery of the heart or brain, causing myocardial infarction or stroke [16].

1.1.2 Cholesterol as a CVD risk factor

Cholesterol is considered a major risk factor of CVD [1, 18]. The notion has come forth through extensive epidemiological and biological research. Cholesterol levels and CHD risk were strongly associated in the Seven Countries Study which later has been referred to as an early epidemiologic evidence of cholesterol as a risk factor of CHD [19]. The Framingham study found that persons with elevated cholesterol levels are more likely to experience CHD [20, 21]. Childhood cholesterol levels also appear to influence future cardiovascular risk. In a
Finnish cohort study of 2229 adults (ages 24-39), intima-media thickness (IMT) of the carotid artery was significantly associated with childhood low density lipoprotein cholesterol (LDL-C), among other risk factors [22].

The widespread notion that elevated cholesterol constitutes a major risk factor of CVD is supported by studies in which cholesterol lowering treatment has had a significant impact on CVD risk [19, 23]. Early evidence that a CHD risk reduction is associated with cholesterol lowering treatment was given by the Lipid Research Clinic Primary Prevention Trial in 1984 [24]. In this trial hypercholesterolemic men were treated with cholestyramine resin which caused an 8% reduction in total cholesterol (TC) and a 10% reduction in LDL-C. The cholesterol reductions were associated with a 16-19% reduction in CHD risk.

More effective reductions in total- and LDL cholesterol levels have come forth through statin treatment. Reducing TC levels and LDL-C levels by the use of statins has been strongly associated with reduction in cardiovascular risk in many large studies [25-27]. A meta-analysis from 2010 that included 170000 subjects showed that reduction in major vascular events was best predicted by total reduction in LDL-C. The conclusion was that each 1 mmol/l reduction in LDL-C decreased the annual rate of major coronary events, coronary revascularization and stroke by one fifth [28]. High levels of childhood LDL-C has been found associated with increased adulthood IMT [22].

**Apolipoprotein B**

Raised level of apo B is considered a possible independent risk factor of CVD by the WHO [1]. Apo B is present in very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), large buoyant LDL and small dense LDL. Each of these atherogenic particles contains one molecule of apo B. Thus, measures of total apo B in an individual reflect the exact number of potentially atherogenic particles. In most conditions, 90% of apo B is found in low density lipoproteins (LDL), the lipoprotein fraction that also carries 70% of the cholesterol in plasma under normal conditions [29].

**High-density lipoprotein**

High density lipoprotein (HDL) is considered cardioprotective as inverse correlations between the cholesterol concentration in HDL and risk of CHD have been found repeatedly [30].
HDL-cholesterol (HDL-C) levels <1.0 mmol/l in men and <1.2 mmol in women serve as markers of cardiovascular risk [31]. Many properties of HDL-C make high levels favorable in terms of cardiovascular health. A 2011 review [32] summarize the anti-atherosclerotic properties of HDL-C. Besides being central in the transport of excess cholesterol from peripheral cells, such as foam cells, to the liver for excretion into bile (“reverse cholesterol transport”), HDL particles possess other anti-atherogenic properties that may be independent of their role in cholesterol homeostasis. Such effects are the abilities to improve endothelial function, reduce vascular inflammation, reduce oxidation and reduce thrombosis [32].

Apolipoprotein A1

Apolipoprotein A1 (Apo A1) is the major apolipoprotein in HDL particles. Apo A1 initiates reverse cholesterol transport, as it can bring excess cholesterol back from peripheral cells to the liver. Reviewing the suggested actions of apo A1, scientific evidence also suggests it displays anti-inflammatory and antioxidant effects [33]. In most cases, apo A1 only reflects the athero-protective part of cholesterol metabolism, as is it not a part of apo B lipoproteins [33]. Low Apo A1 has been found to be a risk factor of myocardial infarction [34].

Apo B/Apo A1

The ratio between apo B and apo A1 has shown to function as a predictor for risk of myocardial infarction [6, 35] and to be associated with stroke [36], with higher apo B/apo A1 ratios indicating higher risk. The AMORIS study, a prospective study that included more than 98000 men and 76000 women, found the apo B/apo A1 ratio and increased risk of fatal myocardial infarction to be strongly and positively related in both sexes [34]. Out of nine important risk factors of CHD, the INTERHEART study found the apo B/apo A1 ratio to be the single risk factor that best predicted myocardial infarction [6].

Triglycerides

The relation between triglycerides (TG) and risk of CVD has been debated [18, 37]. Possible harmful effects of raised TG may be increased levels of atherogenic lipid remnant particles, small dense LDL or an association with low HDL-C levels. Genetics, obesity, and a diet rich in carbohydrates are among probable causative factors of raised TG. New data support a causal relationship between TG and risk of CVD through TG mediated pathways of lipid
metabolism [38], and a recent AHA Scientific Statement characterizes TG as an important biomarker of CVD risk because of its association with atherogenic remnant particles. However, the statement reaffirms that TG is not directly atherogenic[37].

**CRP**

C-reactive protein (CRP) production is a part of the nonspecific acute phase reaction to most forms of inflammation, infection and tissue damage [39]. Circulating levels of CRP has been found in positive association with risk of CVD in prospective studies in adults, and proposed evidence indicate that CRP is associated with events of CHD [40, 41]. However, the role of CRP as an independent causal factor for the initiation of atherosclerosis may seem controversial [42], and evidence that reducing CRP levels prevents CHD is lacking [41]. CRP may however be a marker of increased cardiovascular risk that is influenced by other independent risk factors of CVD [42]. Whether childhood CRP reflects increased vascular inflammation in children is a field of inspection. The young Finns Study found no significant associations between childhood CRP and adult IMT, but childhood CRP levels weakly predicted adult CRP levels [22].

**Lp(a)**

Strong associations between high levels of lipoprotein (a) (Lp(a)) and increased risk of CVD indicates that Lp(a) is a causative factor of premature CVD. The harmful effects may be caused by either pro-thrombotic or anti-fibrinolytic properties, or by mechanisms resembling those of LDL in atherosclerosis, as Lp(a) is a cholesterol-rich particle, or both [43]. The particle is formed by the linking of a LDL-like lipoprotein by a disulfide bridge to apo(a). The plasma level of Lp(a) is to a large extent genetically determined, not a direct subject of lifestyle treatment and described as relatively resistant to lipid lowering strategies [44]. However, with high Lp(a) levels optimizing in other areas related to cardiovascular risk may be regarded as important measures. Measuring Lp(a) is suggested in high- and intermediate CVD risk patients. A single measure is considered sufficient [43], as levels of Lp(a) appears stable over time [45]. A frequently used reference value of Lp(a) is <300 mg/L, [46, 47], with 75% of the population having Lp(a) levels within this range [46] although values may be thousand fold [44]. Lp(a) levels above 300 mg/L have been related to increased risk of CVD [47, 48].
1.2 Diet and cardiovascular disease

1.2.1 Relations between diet and cardiovascular disease

Traditional analyses in nutritional epidemiology have typically examined diseases in relation to single nutrients. Numerous studies have examined the relationship between single nutrient intakes and the risk of CHD [49]. Such analysis has been quite valuable, although with some conceptual and methodological limitations. One important limitation is that the effect of a single nutrient may be too small to detect. Another limitation is that people do not eat isolated nutrients, but meals consisting of a variety of foods where nutrients may interact or act synergistic [50].

A different way of investigating the relationship between diet and cardiovascular disease is by studying CVD in relation to different dietary patterns. Several studies have used this approach the last decades [6, 51-56]. Dietary patterns have gained emphasis as research objectives in nutritional epidemiology, as the limitations regarding single nutrient research have been increasingly recognized. A rationale for the implementation of dietary patterns in nutritional epidemiology is that investigations of dietary patterns parallel more closely to the actual dietary intake than single nutrient investigations do, as they include the possible joint effects of nutrients [57] [50]. The cumulative effects of multiple nutrients in a dietary pattern may be large enough to be detectable, underpinning the use of dietary patterns as objectives in epidemiologic trials [57, 58].

1.2.2 Dietary patterns and prevention of CVD

Systematic knowledge reports have concluded that there are convincing causal relationships between certain dietary patterns and cardiovascular risk. Examples are “a prudent diet” and vegetarian diets, that have both been found to improve risk of CHD, and the DASH diet that improves risk of high blood pressure [57].

Less favorable is the “Western” diet [59]. The pattern is characterized by high intakes of red meat, processed meats, high fat dairy products, eggs, refined grain products and sugared foods and drinks, and low in intakes of fruits and vegetables, whole grain products and fish [57]. The fatty acid composition of a Western diet is frequently unfavorable, with excessive saturated and trans-fatty acids [59]. The majority of saturated fatty acids present in Western
diet are the stearic acid (18:0) that does not affect LDL-levels, but also palmitic acid (16:0) shown to increase LDL-C [60].

The contribution from different types of fat appears to be the critical factor of dietary fat influence on cholesterol. Dietary patterns with high contents of unsaturated fatty acids have shown a favorable role of those fatty acids on cardiovascular risk. When poly- and monounsaturated fatty acids replace SFA in metabolic studies, TC, LDL-C and TG are reduced [55, 61]. High ratios of non-saturated fatty acids to SFA has shown inverse associations with risk of CHD [52]. Fish provides long polyunsaturated n-3 fatty acids, compounds that have been related to lowered risk of CVD and cardiovascular death [62, 63].

The Mediterranean diet is rich in unsaturated fats, with the main source of dietary fat being olive oil. Red meat is consumed only in small doses while intakes of fish and poultry is somewhere between medium and high. Cheese, yoghurt and eggs are consumed in moderate amounts. The Mediterranean diet is rich in plant-based foods such as fruit, nuts, vegetables, potatoes, legumes and whole grain products [57]. Large scale studies have shown the Mediterranean diet to be a dietary pattern that reduces risk of CHD [52, 53].

The high content of vegetables and fruits in the Mediterranean diet is considered beneficial. Many large prospective studies have shown promising effects on CVD risk from diets rich in vegetables [64-67]. In the Physicians’ Health Study, men who consumed more than 2.5 servings of vegetables per day had a relative risk of 0.77 for CHD compared to the man who consumed less than 1 serving per day [66]. In a follow up study of the Physicians health study and the Nurses’ Health Study, those who belonged to the highest quintile of fruit and vegetables intake had a RR of 0.69 of stroke, compared to those in the lowest quintile. The median intake in the highest quintile of women was 5.8 servings a day and 5.1 servings a day in that of men [67]. The exact mechanisms of fruit and vegetables on CVD risk are still unknown. Proposed mechanisms are among others the providence of phytochemicals such as folate, potassium, antioxidants and fiber [64].

Fruits and vegetables in large amounts is also a characteristic of the DASH diet, that besides is high in low fat dairy products and low in total fat and saturated fats. This diet has shown to reduce blood pressure [54]. This has also been associated with a “prudent diet” in which fish, fruits, vegetables and berries, legumes, poultry and whole meal foods are important parts of diet, besides low intakes of high fat dairy products, animal fats and cholesterol rich foods as
eggs and shellfish. When such a diet provides 25-35 % of total energy, < 7% of total calories from SFA and less than 200 mg cholesterol it has shown to reduce risk of CHD [68].

Recently, beneficial effects on LDL-C and systolic blood pressure have been observed in subjects receiving a “healthy Nordic diet” that is based on the Nordic nutrition recommendations (2004) and inspired by principles of the Mediterranean diet and the DASH diet among others. This dietary pattern includes fruits, berries, vegetables, low fat dairy products and oily fish that have their origin and are typical foods consumed in Nordic countries [56]. Whole meal rye, cabbages and root vegetables are specific components of the Nordic diet that have been found associated with reduced mortality when intakes are high [69].

The broad research on relations between diet and CVD has led to the development of strategies to prevent CVD in the general population, including dietary guidelines. The current Norwegian food based dietary guidelines recommend a diet rich in vegetables, fruits and whole grain. Furthermore, low fat dairy products are recommended as part of the diet. Fish intake should be equivalent to 2-3 dinner portions per week, out of which 2 should be oily fish. Choosing lean meats is recommended, as well as oils, soft- and liquid margarines. Intakes of sugar and salt are recommended limited [57]. The Norwegian dietary recommendations are much in line with The American Heart Association dietary recommendations [70].

1.3 Dietary assessment

Nutritional influence on the occurrence of human disease may be considered a particularly challenging field of epidemiology, as diet appears with a complex nature. Unlike many disease provoking factors that one can consider present or absent and easily measurable regarding the degree of exposure, diet consists of a range of components that are strongly interrelated. Besides, clear changes in diet are rarely observed at specific points in time, as dietary patterns evolve over years. Furthermore, measures of nutrient intake have to be done in an indirect fashion through the registration of food consumption, as individuals generally are not aware of what their food contains [50].
1.3.1 Recording methods

Information about peoples’ dietary habits and intake of food can be obtained by different methods. Recording methods include weighed- and unweighed food intake record. In both cases every item that is consumed is recorded, usually for 3-7 days. The former requires that amounts of foods and drinks are weighed or measured and the amounts recorded. The latter does not include measuring weight of foods, but amounts are described as accurately as possible. In both cases, the records are analyzed by use of computer programs to assess nutrient intakes. Weighed food intake record involves a lot of work for subjects and investigators, and is an expensive method requiring time and appropriate equipment. However, the method provides the most precise quantitative measurement of intake and is often referred to as the “gold standard”. Unweighed food record is not as demanding to the participants and generally more acceptable, as food is not weighed. However, problems with this method may include the interpretation of portion sizes, and that this method requires much work and resources from the researchers as well [71].

1.3.2 Recall methods

Recall methods are retrospective as they depend on the subjects recalling their consumptions of foods and beverages. Assessment of actual intake involves asking subjects to recall in detail what they have consumed the previous 24 hours. Day to day variation of diet is not captured by this method, but one advantage of the method is the flexibility of performance regarding time and place. Alternatively, repeating the method over days may give a more holistic presentation of diet.

Recall methods may also measure usual diet by the method of diet history. The method includes a 24-hour recall followed by questions to assess what constitutes usual meals throughout the day in general, so that a food intake pattern is eventually built by means of descriptions. The last stage of the method involves going through a list of foods with the subject, to cross-check the information that has been obtained [71].

A frequently used method for registration of usual diet is also the food frequency questionnaire (FFQ). The FFQ is a recall method that measures habitual food intake, based on the frequency of consumption of certain food groups. The underlying rationale of the FFQ is that average long term diet is the conceptually important exposure of diet, instead of the exact
intake on a few days [72]. The FFQ contains a list of foods and drinks that the subjects are asked to record how often they consume. Usually, the frequency is expressed as “times per week” or “times per month” [73]. When questions about amounts of food are also included, the questionnaire is called a semi-quantitative FFQ. The FFQ can be used as a self-administered questionnaire or as a personal interview. The method gives less precise information than recording methods, but often donates a more representative picture of habitual intakes than exact recordings of a few specific days. FFQs have been used in large scale studies to investigate relations between diet and disease risk. Attempts to look at dietary patterns and develop scores of diet quality have also been made. In addition, FFQs can also be used for clinical purposes by serving as templates for dietary assessment when giving dietary advice [71].

1.4 Familial hypercholesterolemia

Familial hypercholesterolemia is an inherited disorder, characterized by elevated blood cholesterol and premature ischemic heart disease. FH is one of the most prevalent monogenic diseases known, affecting as many as 1/500 globally. While this number reflects the relatively frequent occurrence of heterozygote FH, the prevalence of homozygotes is only 1/1000000 [74]. The prevalence of FH varies among countries and ethnicities [75]. In Norway the estimated prevalence of heterozygotes is approximately 1 in 300 [76]. The diagnosis was formerly made based on whether the patient met certain diagnostic criteria concerning history of premature coronary artery disease, raised LDL-C and presence of lipid depositions in patient and/or first degree relatives. The criteria are increasingly being replaced by genetic testing to confirm the diagnosis. Because physical manifestations of the disease are rarely present in children with FH, genetic testing is recommended as the main diagnostic tool. When the mutation cannot be traced, LDL-C levels >3.5 mmol/L and total serum cholesterol >5.5 mmol/L are recommended to diagnose children and adolescents [77].

FH has been extensively described and has a rich history in the field of genetic epidemiology [19, 75, 78]. In the late 19th century, children with clinical symptoms resembling what is now known as features of FH were described by Lehzen and Knauss [19]. In 1939, the Norwegian professor Carl Müller described observations from 17 Norwegian families and suggested inheritance of dominant quality [79]. Throughout the 70s and the 80s frequent research activity cumulated in Goldstein and Browns discovery of the LDL-receptor [80] as the
causative gene of FH [19, 78, 80]. Today, more than 1000 different LDL-receptor gene variants from FH patients have been reported [81], as well as some other mutations affecting proteins involved in the LDL-receptor-ligand binding and LDL-uptake[78]. Rare autosomal recessive forms have also been identified [82]. Scientific evidence suggests that different mutations may lead to different extent of cholesterol elevation and risks of cardiovascular disease [83, 84]. In heterozygotes measured level of TC may be 2-3 times the levels of that in individuals without FH. Homozygote FH patients may have TC values that are 5-6 times the mean observation in healthy individuals [85].

1.4.1 The genetic basis of FH

Functional LDL-receptors in the liver and elsewhere are prerequisites of normal plasma clearance of LDL, intracellular transport of cholesterol and cholesterol catabolism. Usually, FH is caused by a mutation in the LDL-receptor gene, but some other mutations have also been found to cause FH. Mutations in apo B may disrupt the ability of LDL to bind to the LDL-receptor, and other rare causes of FH are mutations in the PCSK9, a sterol regulated gene [78].

The LDL receptor

The LDL-receptor is responsible for the uptake of LDL from the bloodstream into cells. As much as 75% of the LDL-receptors are localized in the liver, although the receptor is widely distributed throughout the body [85]. Normally, LDL binds to the LDL-receptor and the LDL-LDLR complex becomes internalized into the cell through endocytosis. Inside the cell, the endosomes fuse with lysosomes that degrade the LDL particles, releasing cholesterol. When the cholesterol concentration in the cell is altered, it affects production of LDL-receptors and endogenous cholesterol synthesis, in order to maintain cholesterol homeostasis [74, 80, 85].

The mutated LDL receptor gene in FH

In familial hypercholesterolemia, plasma clearance of cholesterol, intracellular cholesterol transport and cholesterol catabolism is hampered as a result of the FH mutation. LDLR mutations can be divided into different functional classes depending on their phenotypic effects on the receptor [80, 83, 86]. Class 1 mutations fail to produce the LDL-receptor. Class 2 mutations produce proteins that are transportation defective, as their transportation between
endoplasmic reticulum and Golgi is blocked, either completely or partially. The class 3 mutations produce LDL-receptors that reach the cell surface, but fail to bind LDL. LDL-receptors of class 4 mutations bind LDL, but then fail to internalize the lipoprotein. Class 5 mutations bind LDL on the cell surface and internalize, but the LDL receptor fails to discharge the ligand in the endosome. As a result, the receptor is not recycled to the cell surface [86].

1.4.2 Clinical features of FH

Increased risk of CVD

FH mutations cause increased levels of cholesterol in affected subjects. The increased levels of LDL in FH-patients contribute to accelerated formation of atherosclerosis and increased risk of developing CVD. If treatment is not implemented, manifest CVD may come forth at an early age. Untreated, the majority of affected men and women will have symptomatic coronary disease by the age of 60, and 15% of the women and 50% of the men will have died [18]. Although the FH-mutation constitutes the basis that leads to increased cholesterol levels in FH, the influence of environmental factors such as diet should not be underestimated, as people with the same FH mutation, but living in very different environments, have shown significant differences in cholesterol [87].

Early signs of atherosclerosis

The progression of atherosclerosis in childhood appears to be more severe in FH-children than in normocholesterolemic children. This is supported in part by findings regarding inflammation and increased intima media thickness. It has been demonstrated that FH-children and healthy children differ in their gene expression of the chemokine “regulated on activation normally T-cell expressed and secreted” (RANTES) in peripheral mononuclear blood cells. This may contribute to inflammation and premature development of atherosclerosis in FH children [88]. In FH-children an inflammatory imbalance between tumor necrosis factor α and interleukin-10, that links to the accelerated atherosclerotic process has been observed [89]. Carotid ultrasound measurements of FH-children and healthy children further support the notion of premature risk of CHD. Comparison of carotid intima-media thickness (CIMT) have shown differences in CIMT between FH affected and non-
affected siblings from the age of 10 and onwards [18]. Similar results have been detected between other age matched FH-children and healthy children in the age of 10-19 years [90]. Increased plasma CRP levels have been found in children with FH [91, 92], but the findings are inconsistent, with recent findings suggesting that other inflammatory biomarkers may better reflect systemic inflammation in this group [89].

**Physical signs of FH**

Physical signs due to lipid depositions in tendons, eye lids and the eye (figure 1) are characteristic features of FH. In the heterozygote phenotype the manifestations are usually not readily apparent until the age of 25-30 years. Generally, tendinous manifestations are the most frequent. The homozygote phenotype, which involves much more severely affection, is characterized by the addition of cutaneous manifestations, usually evident before the age of 10.

Tendinitis may occur frequently as cholesterol depositions in the tendons may lead to inflammation and pain. Thickening of the Achilles tendon is a typical clinical sign of FH. Lipid depositions on tendons are called tendon xanthomata. Sometimes lipid depositions form in the extensor tendons to the fingers, and rarely elsewhere in the body.

Physical signs may also be evident in and around the eyes. A white line on the cornea of the eye may show. This deposition of lipid is referred to as an arcus cornealis. Flat yellow plaques referred to as xanthelasma, may be evident in the eyelids. Xanthelasma are not necessarily a sign of FH, as they are not FH specific, but may even present in persons with normal plasma lipoprotein values [93].
Figure 1. Characteristic clinical features of FH; a: xanthomata on the Achilles tendon; b: xanthomata on Tuberositas Tibiae; c: arcus cornea; d: xanthomata on the dorsum of the hand; e: xanthelasms above eyelid. All pictures are used with permission from owner Kjetil Retterstøl (a, b, d, e) and Leiv Ose (c).

1.4.3 Influence of maternal or paternal heredity

The possible influence of the in utero environment on susceptibility of disease later in life, has been the research objective of many research projects since Barker and his colleagues first established their “thrifty phenotype hypothesis” [94, 95].

Pregnant FH women have higher cholesterol levels than healthy women, and they have been found to have enhanced endothelial activation [96]. Their condition may possibly expose the fetuses to more atherogenic environments [97]. The Fate of Early Lesions in Childhood (FELIC) study, performed on non-FH children, found that maternal hypercholesterolemia during pregnancy is associated with fatty streaks in the offspring that could predetermine the progression of atherosclerosis throughout childhood [98]. Besides, the hypercholesterolemic mothers showed elevated CRP levels that correlated significantly with atherogenesis in the
children[99]. On the other hand, IMT in FH-children that inherited the disorder maternally compared to those who inherited FH from their father, has been found not to differ[100]. Still, children that have inherited FH maternally may be more prone to atherosclerosis, as it has been found that maternal familial hypercholesterolemia increases adult TC, LDL-C and apo B, in comparison with paternally inherited FH [101]. Recent findings also suggests higher excess mortality rates in untreated FH subjects that have inherited the disease from their mother, compared to those who have inherited it through their father[102].

1.4.4 Treatment of FH

The treatment of FH involves drug treatment, dietary guidance and guidance concerning lifestyle factors related to CHD such as diet and physical activity [18, 31, 103-105]. The treatment depends on age and maturity of the patient. Dietary guidance applies to all patients, while drug therapy is usually not initiated until sometime between the ages of 10 and 18 years, although the age at which to start drug therapy is a matter of clinical judgment [18]. Specialist guidance on proper treatment, as seeking a lipid clinic, is a repeated advice in treatment guidelines [18, 103]. Initiation of such treatment before clinical coronary artery disease has developed may lead to normal life expectancies in FH patients if treatment is well managed [106], and is therefore of great importance.

Lipid lowering drug therapy

Statins are cholesterol lowering drugs that exert their effect by inhibiting HMG-CoA reductase, the rate limiting enzyme in cholesterol synthesis. Reduced intracellular cholesterol concentrations increase the synthesis of LDL-receptors causing greater uptake of LDL and other apo B containing lipoproteins from the blood [18]. Statin treatment may lower LDL-C by 18-55 %, TG by 7-30% and increase HDL-C by 5-15 % [105] in a dose-dependent manner. In adult FH patients, statin therapy has shown to improve clinical outcome [106, 107]. Evidence from CIMT measuring in hyperlipidemic patients has shown that statin therapy reduces the rate of plaque formation in the carotid artery [108, 109], supporting early initiation of statin therapy, as this is related to reduced cardiac risk. Statin treatment is now recommended in late childhood or adolescence [18]. Evidence from statin research in children with FH has shown efficacy and safety of statin treatment in line with that of adults [104], albeit there have been no long-term outcome studies in children [110].
In severe cases of FH, combined drug therapy may be indicated. Ezetimibe is the drug most frequently used in combination with statins. The substance inhibits dietary and biliary cholesterol absorption, reducing LDL-C by 15-22% in hypercholesterolemic subjects. Other cholesterol lowering drugs are bile acid sequestrants that may add a further 10-20% reduction in LDL-C when combined with statin therapy [18].

**Lipid treatment goals**

Risk of cardiac disease varies with lipid levels in a continuous fashion. Meanwhile, the presence of other risk factors substantially influences the impact of lipid levels on CHD risk. As a result, absolute limits of what constitutes optimal or harmful lipid levels are not appropriate. However, as guidance, the Norwegian national guidelines on primary prevention of CVD proposes specific general treatment goals in hyperlipidemias, with the important noting that more ambitious treatment goals may apply to FH patients especially, as they have been exposed to high levels of atherogenic lipids through their whole life and are considered high risk patients[103]. For the same reasons, the 2011 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias [18] propose treatment goals of LDL-C to be < 2.5 mmol/l, with the additional recommendation of LDL-C < 1.8 mmol/l in patients with established CHD. Recommended targets of apo B are between 0.8 and 1.0 g/L. Treatment goals are not defined for HDL-C and TG [18], but the Norwergian guidelines suggests that levels of HDL-C below 1.0 mmol/l in men and below 1.3 mmol/l in women, as well as TG of less than 1.7 mmol/l, as satisfactory values in primary prevention in hyperlipidemias[103].

The American Heart Association has outlined guidelines aimed especially at the treatment of children and adolescents with FH. Initially, a fat and cholesterol restricted diet is recommended, aimed at reducing LDL-C to at least 4.9 mmol/l or 4.1 mmol/l if there is a positive family history of CHD. If these treatment goals are not achieved by dietary adjustments in children aged 10 years or older, cholesterol lowering drug treatment is indicated. The minimal LDL treatment goal in drug therapy for children and adolescents is LDL < 3.35 mmol/l, whilst the ideal LDL treatment goal is < 2.85 mmol/l. Presence of additional CHD risk factors may indicate even lower cut points for drug therapy, indicate statin treatment before the age of 10 years and lower the treatment targets and [104].
Dietary treatment

Dietary adjustments to lower cholesterol have known effects in patients with non-familial hypercholesterolemia, as a total cholesterol reduction of 10-30 % has shown achievable \cite{111, 112}. As an adjuvant to lipid lowering drug therapy, dietary treatment is recommended to all FH patients \cite{104, 105}. The principles of a cholesterol-lowering diet in FH includes reductions in total fat intake, reductions in the intake of saturated fatty acids, reduced intake of cholesterol and may also include manipulation of carbohydrate intake to replace the energy deficit of the low fat diet \cite{113}. Studies have shown that saturated fatty acids as a whole, and trans fatty acids, decrease LDL-receptor mediated catabolism and thereby increase LDL-cholesterol, albeit in animal studies and studies of humans without FH \cite{60, 114}.

The American National Cholesterol Education Programme (NCEP) has proposed specific nutrient composition recommendations for diet as a part of therapeutic lifestyle changes in LDL-lowering therapy. The recommendations are summarized in table 1.

Table 1. Nutrient composition of the therapeutic lifestyle changes diet, adapted from the NCEP Adult Treatment Panel III \cite{105}

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat*</td>
<td>&lt;7% of calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
</tr>
<tr>
<td>Total fat</td>
<td>25%-35% of total calories</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50%-60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20-30 g/d</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/d</td>
</tr>
<tr>
<td>Total calories</td>
<td>Balance energy intake and expenditure to maintain desirable body weight / prevent weight gain</td>
</tr>
</tbody>
</table>

* Trans fatty acids should also be kept at a low intake

In dietary treatment of patients with increased risk of developing CVD, all individuals should be advised about food choices that are associated with lower CVD risk. Some overall principles of dietary treatment are that general recommendations should suit the local culture \cite{18, 31} and that a wide variety of foods should be eaten. Fruits, vegetables, wholegrain
cereals and bread, lean meat, low fat dairy products and fish, especially oily fish should be encouraged choices of food [31, 103]. Vegetable and marine sources of fat should be used to replace saturated fats, together with the already mentioned foods [31]. Furthermore carbohydrates should primarily be derived from foods rich in complex carbohydrates, such as grains and whole grains, fruits and vegetables [105].

Margarine containing plant stanols/sterols may be used, with the maximum cholesterol lowering effect observed in hypercholesterolemic patients at intakes of 2 g sterols/stanols per day. Cholesterol reductions in children and adults seem to be the same in response to daily consumption of 1.8-3 g plant sterols. When added to a low fat diet, 2 g/d of plant sterols may reduce LDL-C by 9 % in hypercholesterolemic patients [115].

**Effects of lipid lowering diet in familial hypercholesterolemia**

Apparently, few trials have been performed to investigate effectiveness of lipid lowering diets in children or adults with familial hypercholesterolemia and consensus has yet to be reached regarding what actually constitutes the most appropriate dietary treatment in this patient group[113].

Some have investigated potential cholesterol reducing effects of adding specific food components or nutrients to an already “lipid lowering diet”. In a trial on children with FH, daily consumption of margarine containing 1.2 g plant sterol in combination with a low fat diet, reduced LDL-C by 11 % compared to a low fat diet alone [116]. Similar results have been found elsewhere [117]. However, the evidence of efficacy and safety of plant sterol treatment in children with FH may be considered insufficient in terms of stating recommendations [113, 118].

Soya has also been a target of investigation [119]. However, inconsistent findings and scarce data on the issue makes the potential effects of soya on cholesterol an unconcluded area [110, 113, 120]. Interventions where n-3 fatty acids have been added to cholesterol-lowering diets have also been performed in children and adults without obtaining significant reductions in cholesterol [121, 122].

A Cochrane 2010 review aimed to examine whether a cholesterol-lowering diet is more effective in reducing heart disease and lowering cholesterol than no dietary intervention in children and adults with FH [113]. Only eleven studies met the criteria of the review, which
made the total number of participants in the review 331. The authors concluded that no conclusions could be made about the effectiveness of a cholesterol lowering diet in this patient group. Similarly, Norwegian national guidelines of individual primary prevention of cardiovascular disease stated their inability to evaluate the effectiveness of dietary treatment in familial hypercholesterolemia due to lack of good data [103]. To our knowledge, investigations regarding the effectiveness of the dietary treatment in this particular patient group are scarce, and only very few studies have investigated relations between diet and cholesterol levels in children with familial hypercholesterolemia. Yet, dietary treatment is the primary treatment measure in children with this disease.
2 Aims of the study

This thesis aims to investigate relations between diet and blood lipids among children with familial hypercholesterolemia by use of the SmartDiet questionnaire and to compare aspects of their diet to that of non-FH children. Further, the thesis aims to investigate if diet and cholesterol levels in young FH subjects are influenced by parental inheritance of FH.

2.1 Specific objectives of this thesis

Specific objectives of this thesis are

1) To investigate the difference in dietary score as a measure of healthy diet between children with familial hypercholesterolemia and non-FH children by the use of the SmartDiet Questionnaire.

2) To characterize food choices among children with familial hypercholesterolemia regarding some important components of a heart protective diet, and to compare the food choices to that of non-FH children.

3) To investigate if there are correlations between the SmartDiet scores and the blood lipid levels of children and young FH subjects and non-FH children.

4) To investigate if children and young FH subjects who inherited the disease from their mother differs in SmartDiet scores, blood lipid levels and CRP compared to children and young FH subjects who inherited the disease form their father
3 Subjects and Methods

This project was approved by The Regional Committee of Medical Ethics (see appendix 1).

3.1 Recruitment of participants

3.1.1 FH subjects

Subjects were invited to participate in the period of February to July 2011. Subjects invited to participate were patients diagnosed with FH, attending the outpatient clinic in the period 2000-2010 between the ages of 6-18 in that time-period. Invitations were sent by mail to the address quoted in the hospitals’ patient register. Along with the invitations, that included a short summary of the purpose of the project (appendix 2), there were sent two copies of an informed consent scheme (see appendix 3), a SmartDiet questionnaire (appendix 4) and a short form to identify medication, presence of chronic disease, history of hospitalization and possible presence of cardiovascular disease in the family (appendix 5). The invited subjects also received a prepaid envelope to use when they returned the forms. One copy of the informed consent was to be kept by the subjects’ parents or guardians or by the subject if he/she was 16 years or older. The other copy was to be signed and returned to the Project leaders. The SmartDiet questionnaire was to be completed by the invited subject and returned along with the signed informed consent and the completed medical form in the prepaid envelope.

A total number of 610 patients diagnosed with FH were invited to participate in the study. Out of these, 174 responded. Some of the responses lacked either the signed informed consent or the SmartDiet questionnaire. In most of these cases, subjects were tried contacted by phone, informed about the project and kindly asked to complete and return a new copy that would be sent them after their permission. Whenever the subject was younger than 16, the inquiry was addressed to the parents or guardians. Signed informed consent was missing in 22 of the responses. Among them, 7 could not be contacted because their phone numbers could not be found and 6 persons did not respond to the phone calls. Nine persons responded and agreed on receiving another form. Eight signed informed consents were later returned to the project. (See flow chart.)
Figure 2. Flow chart showing inclusion and exclusion of FH subjects

Nineteen of the initial responses lacked the SmartDiet questionnaire. In 2 of these cases, the subjects’ newest patient records were from 2006 or earlier (an exclusion criterion) and no further attempts were made to obtain their questionnaires. In 3 cases, questionnaires that were completed in connection with the subjects’ latest treatment at the Lipid Clinic were found in the treatment records and used for analysis. In the remaining 12 cases, the subjects were tried contacted by phone. Only two were reached. SmartDiet questionnaires were sent them on their permission and completed forms were later received from both. In total, signed informed consents and SmartDiet-questionnaires were obtained from 146 respondents.

Those who had not been evaluated with blood tests and related medical records at the Lipic Clinic during the past four years were not included in the study. Pregnancy at either the time of blood sampling or the time of food registration was also an exclusion criterion. Pregnancy
was not assumed as long as no information of any current pregnancy was reported in the patient journal at the time of blood sampling or in the response sending from the participant. One subject was excluded due to reported pregnancy, and 4 were excluded as their newest journal notes were from 2006 or earlier.

Among the 141 subjects who passed the inclusion criteria, 54 had one or two siblings within the group. As sibling relationships would cause dependency among participants and possibly affect the results of statistical analysis, 29 subjects were excluded so that none in the remaining group were siblings. This was done by writing down all the ID-codes of the siblings on individual pieces of paper, and then sorting them into their respective sibling pairs or groups. Another master student was asked to pick at random without looking, one piece of paper from each sibling pair and -group. The ID-code that was picked showed who was to remain in the study sample. In total, 112 children and young adults with FH were included in the final analysis.

### 3.1.2 Non-FH children

The non-FH children were enrolled from the project “Importance of diet and inflammation in subjects with familial hypercholesterolemia susceptible for cardiovascular disease” that is an ongoing study at the University of Oslo. Eight graders aged 13 years old from two classes at Kastellet middle school were invited to complete a SmartDiet questionnaire and to deliver blood samples at the Lipid Clinic, Oslo University Hospital. The SmartDiet-questionnaires were completed at home and returned to the project at the day of blood sampling. The children were enrolled January and February 2011. All invited children were handed informed consents schemes to be signed by parent or guardian (see appendix 6). Thirty six children wished to join. Out of these, 29 children both delivered signed consent, the completed SmartDiet questionnaire and gave a blood sample. These 29 were included in the final analysis.

One child in the non-FH children group used a vitamin A derivate. Because of low blood lipids and CRP in this subject, it was assumed that the vitamin A derivate did not influence these parameters. The subject was thus included.
3.1.3 FH children aged 11-15 years

Ages of the included FH subjects varied and not all were children. To achieve a group of FH subjects that was more similar to the group of non-FH children in terms of age, all FH subjects that were aged 11 to 15 years old at the time of the SmartDiet completion, were extracted to form a separate group. The age range of two years older and two years younger FH-subjects was chosen so that the group of FH subjects would not be too small. Besides, we presume that the age difference of two years does not change what makes the lead for habitual diet.

3.2 Materials

3.2.1 Collection of dietary data

**The SmartDiet questionnaire**

Collection of dietary data was done by use of SmartDiet, a short self-instructing questionnaire on diet and lifestyle (see appendix 4). The questionnaire is developed by the Lipid Clinic, Oslo University Hospital, to easily enable individual investigation on diet and lifestyle in clinical settings. The questionnaire is considered especially suitable for gaining dietary information in prevention and treatment of cardiovascular disease, diabetes and overweight in a clinical setting with limited time available. Since 2002, SmartDiet has also been used for research purposes in certain hospitals and colleges [123]. The SmartDiet questionnaire was validated in 2002 [124]. The initial questionnaire was intended to assess the intake of the main contributors of fat, fiber, fruit and vegetables in the usual diet [124] and has later been revised twice to adjust for the food selection. The last revision was in 2009. In 2010, the Lipid Clinic conducted a survey to document the usefulness of SmartDiet in clinical practice. The survey was aimed at patients (n=104) who came for consultation. Out of the 104 participants, 87% answered that their current diet was the same as what they ate the rest of the year, and 3 out of 4 reported that they thought finding the foods that they used of their own in the questionnaire was easy [123].

The SmartDiet questionnaire consists of 21 food questions out of which 14 give points. Possible total scores that can be achieved are 14-41 points. The total score is the basis for an overall assessment of the diet. A total score of 27 points or less provides indication that
improvement should be implemented in many areas of diet, in order to make the diet healthier in terms of heart- and general health. A total score between 28 and 35 points indicates that there are some areas of diet that should be improved to make the diet heart-healthier and generally healthier. Healthy dietary habits are indicated by a total score of 36 points or more (appendix 4).

Average use of certain groups of food is registered, either in a quantitative or qualitative way. With each score giving question, there are 3 or 4 possible response options, each giving scores from 1 to 3 points or 1 to 2 points. Which scores are achieved in case of each response option is indicated by three vertical lines. Response options that have the tick marks placed on the innermost line donate 1 point. The middle line tick marks donates 2 points, while the line to the right holds the response options that are most favorable regarding a healthy diet, donating 3 points.

Score giving questions that assess food quality regard use of milk and dairy products, cheese consumption, meat spreads, meats for dinner, butter/margarine/oil, and bread and cereals. All the mentioned food category questions also include a response option to choose in case the use of that food category is rare. In most cases, the “rare use” option donates 3 points. In the case of milk, rare consumption (defined as less than 1 liter a week in the questionnaire) donates only 2 points, as milk is considered an important source of calcium, and frequent use is considered favorable [124].

If ≥1 liter of milk is used per week, most frequent use of whole milk gives 1 point, low fat milk gives 2 points and skimmed milk gives 3 points. Regarding cream and other dairy products, most frequent use of products with 20 % fat or more gives 1 point, products with 10-20% fat gives 2 points and products with less than 10 % fat gives 3 points [124]. Cheese is also categorized in terms of fat content, with the ones with more than 20 % fat in the category giving 1 point if they are the ones that are most frequently used, those with a fat content of 10-20 % fat in the category giving 2 points, and those with less than 10% fat in a category giving 3 points. The exception is cheese with rapeseed oil and sunflower oil, which has a fat content of 16 %, still giving a score of 3 points because of the low content of saturated fatty acids and the high content of non-saturated fatty acids.

Meats on bread are divided into fat meats (>10% fat) giving 1 point and lean meats (<10% fat) giving 3 points, while meat for dinner is divided into high fat cuts (1 point), medium fat
cuts (2 points) and lean cuts (3 points). Butter and margarine on bread is divided into categories of butter and hard margarine (1 point), soft margarine (2 points) and margarine with highly unsaturated fat (3 points). In the case of fat for cooking, alternatives that consists of more than 70% unsaturated fats donate 3 points, while soft margarine donate 2 points. One point is achieved if butter and hard margarine are the most frequent fats used for cooking.

Two options describe the use of bread and other grain products, besides the option “do not eat bread, crackers or other grain products”. The content of fiber separate the grain products into two groups, with high fiber content products giving 3 points, and products low in fiber giving 1 point.

Score giving questions in which consumption is measured in a quantitative way regards use of fish spread and fish as a supplement for salads, fish for dinner, mayonnaise spreads, fruits/berries/vegetables, sweet spread/sweet drinks and snacks. Intakes of fish, mayonnaise spreads and snacks are registered as weekly consumption, while in the case of vegetables, fruits and berries and sweet spreads/sweet drinks, daily consumption is registered. The response options concerning weekly and daily use are to be retrieved in the SmartDiet questionnaire (appendix 4), with their scores corresponding to the scoring system described in a previous section.

Questions that comes in addition to those that lead to the SmartDiet score investigate whether one use a product containing plant sterols, whether legumes, nuts/almonds and avocado are eaten on a weekly basis, how many eggs, cooking included, one eats per week, portions of rice, potato or pasta that is consumed daily and how many amounts of alcohol one consumes per week. Five supplemental questions regarding anthropometrical measures, physical activity, smoking, snuff and use of supplements, including fish oil, are also a part of the questionnaire.

3.2.2 Procedure for registration of dietary data

Calculation of SmartDiet scores

The total score on the SmartDiet was calculated by hand as it is in clinical settings. Each total score was calculated twice to ensure that the correct score was registered. In cases where the participant had ticked more than one option to a question, the mean score of the ticked
alternatives was calculated and used in the calculation of total score. The exceptions were in cases where the respondent had ticked for rare use and another option in the same question. In these cases, the tick for rare use was the only one that was accounted for. Total SmartDiet score was not calculated in cases where response to one or more score giving question was lacking.

**Registration of food frequencies**

To find out which types of food were used more and less frequently among the FH subjects and the non-FH subjects, all the subjects’ responses to the different questions in the SmartDiet questionnaire were registered. In most cases, the subjects’ responses to each question were categorized in accordance with the response options that already exist in the questionnaire. Regarding the use of fish for dinner, the alternative responses fish for dinner “2 times a week” and “3 or more times a week”, were registered as “fish for dinner 2 or more times a week”. Similarly, the alternatives fish spread on “2-4 slices a week” and on “5 or more slices a week”, were categorized into one group of “fish spread on 2 or more slices a week”. The response alternatives regarding vegetables, fruits and berries were also assembled into two categories so that consumption of less than 2 portions a day was one category, and consumption of 2 or more portions a day was a separate category. Regarding omega-3 dietary supplements, cod liver oil and fish oil/omega-3 capsules were assembled in the common category “uses supplement containing omega-3”.

In cases where a subject had ticked for both a seldom use and a food category as the answer to a question, rare use was the alternative that was registered. In cases where a subject had ticked for two or more alternatives of food to answer a question, the answer was not accounted for.

**3.2.3 Collection of clinical and biochemical characteristics**

The clinical and biochemical data on the FH subjects was retrieved from their individual patient records at the Lipid Clinic. Medical records with belonging blood sample reports for use in the data material were selected so that the time gap between the blood sampling and the dietary registration was made as small as possible. Seventy-five % of all blood samples that were used in the data material had been taken prior to the SmartDiet completion, and 25 % afterwards. The average time discrepancies were 1.1 years prior to the SmartDiet completion, and 2 months after the completion, with maximum ranges of 3.9 years and 10 months,
respectively. Forty-six % of the blood tests were within 6 months from the SmartDiet registration, 61 % within a year, and only 9 % of registrations were more than 2 years apart. In all, the average time-space between dietary registration and blood sampling was 45 weeks.

Clinical data from journal notes included statin treatment, any other use of medications, clinical manifestations of FH, information on other chronic disease and which parent carried the FH mutation. In many cases, the information on the last two mentioned variables was retrieved from older journal notes. (Besides attempts to register blood pressure, family history of CVD, number of siblings with FH and educational status and profession of the affected parent was carried out. Because of inconsistent journal data on these variables, they were not usable for statistical analysis.) Use of medications was registered in terms of prevailing statin and other drug treatment at the time of the blood sampling.

Biochemical parameters that were collected from the medical records included TC, LDL-C, HDL-C, apo B, apoA-1, TG, CRP and Lp(a). Apo B/apo A1 ratio was calculated from the obtained values. Eighty-four % of blood samples had been analyzed at Department of Medical Biochemistry, Oslo University Hospital, with the rest analyzed at Medpace (7 %), Covance (3.6%) and laboratories of different Norwegian hospitals (5.4%). The blood sample analyses were made from diverse laboratories as some were sent from local hospitals prior to the patient treatment and others were taken not only in connection with treatment but also for use in international research projects.

In the case of Lp(a), the registered value was not always retrieved from the same blood sample as the rest of the biochemical parameters. However, the Lp(a) measure that was closest in time with the dietary registration was always used.

As CRP values were often given as <1 or <0.6 and Lp(a) values as <300, <100 or <60 precise values of these parameters were often unavailable. In these cases, the values used for estimations were 1, 0.6 and 300, 100 and 60 respectively.

Blood samples from the non-FH children were all collected at The Lipid Clinic, Oslo University Hospital, and analyzed at Department of Medical Biochemistry, Oslo University Hospital. All blood samples were collected within three weeks after the completion of the SmartDiet questionnaire, except in two cases where both were performed on the same day and
in one case where the questionnaire was handed in one week later. Any use of medications was recorded at the time of blood sampling.

### 3.3 Statistical methods

Statistical analyses were performed using SPSS version 19.0, except for Fisher’s exact test that was performed in SPSS Statistics version 18.0 for Windows, as performing this test was not possible in the 19.0 version in some cases.

A p < 0.05 was considered statistically significant.

Histograms and Q-Q plots were used to evaluate whether data was normal distributed. Normal distributed data were presented as mean and standard deviation, while data that were not normal distributed were presented as median and quartiles (25th and 75th percentiles, Q1, Q3). When comparing two groups that both were normal distributed, the independent samples t-test was used. Otherwise, Mann-Whitney U test was performed. To verify results of statistical significance when data was more or less normal distributed, both types of test were performed. When extreme values were observed, tests were performed with and without them to find out if they had impact on the p-value regarding significance. When outliers were observed in cases of independent samples t-test, the tests were performed both with and without them. When the removing of extreme values or outliers affected the p-value regarding significance, this is noted in the text or table text.

Associations between continuous variables were investigated by means of Spearman’s rank correlation coefficient. This was used as Spearman’s rank correlation coefficient is less sensitive to outliers compared to Pearson’s correlation coefficient.

Categorical variables were presented as count with percentage.

When differences in categorical variables were measured, such as use of different food groups, Chi-square test for independence was used, or Fisher’s exact test when the assumptions for using Chi-square test were violated.

Some values were missing from medical records, blood tests and SmartDiet questionnaires. To keep the sample size as big as possible, pairwise exclusion of cases was chosen instead of listwise.
4 Results

4.1 Reported food intake in children and young FH subjects and in non-FH children

4.1.1 Characterization of the children and young FH subjects and the non-FH children

Characterizations of the 112 FH-subjects, and characterization of and comparison between the 43 FH subjects aged 11-15 years and the 29 non-FH children are shown in table 2. Median age of the total FH group, the FH subjects aged 11-15 years (FH (11-15)) and the non-FH children on date of SmartDiet completion were 15, 14 and 13 years respectively. Age of the non-FH children was significantly lower than that of the FH children aged 11-15 years. As expected on basis of the diagnosis, the FH (11-15) group had significantly higher levels of TC, LDL-C, apo B and higher apo B/apo A1 ratio. No other parameters showed significant differences. Lipid levels of the non-FH children were all within reference values.

Among the total FH-group 41% were statin treated, and ~4% were additionally treated with other lipid lowering drugs. Among the FH children aged 11-15, 23% received statin treatment. Characterization and comparison of the subjects receiving and not receiving statin treatment is shown in table 3. Age was significantly higher in the statin treated group. Clinical manifestations of FH were only present in subjects that were statin treated, with tendinitis being the most frequent, albeit rare. In line with what one would expect, statin treated subjects had significantly lower levels of TC, LDL-C, apo B and apo B/apo A1 ratio. No other differences were observed.
Table 2. Characterization of all FH subjects, FH children (11-15) and non-FH children, with comparison of the FH children (11-15) and the non-FH children.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All FH subjects (n=112)</th>
<th>FH (11-15) (n=43)</th>
<th>Non-FH (n=29)</th>
<th>p&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>112 15 (12 - 18)</td>
<td>43 14.0 (12.0 - 14.5)</td>
<td>13 (13 - 13)</td>
<td>0.01&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>112 65 (58%)</td>
<td>43 22 (51%)</td>
<td>11 (38%)</td>
<td>0.39&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>112 46 (41.1%)</td>
<td>43 10 (23.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other lipid lowering drugs</td>
<td>112 4 (3.6%)</td>
<td>43 0 (0.0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthomas</td>
<td>108 2 (1.9%)</td>
<td>43 0 (0.0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xanthelasms</td>
<td>107 1 (0.9%)</td>
<td>43 0 (0.0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arcus cornea</td>
<td>108 0 (0.0%)</td>
<td>43 0 (0.0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>107 3 (2.8%)</td>
<td>43 1 (2.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thickened heal tendons</td>
<td>108 2 (1.9%)</td>
<td>43 0 (0.0%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>112 6.4 ± 1.5</td>
<td>43 6.6 ± 1.6</td>
<td>3.8 ± 0.6</td>
<td>&lt;0.001&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>111 4.43 ± 1.4</td>
<td>42 4.7 ± 1.4</td>
<td>2.1 ± 0.5</td>
<td>&lt;0.001&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>112 1.4 ± 0.3</td>
<td>43 1.3 ± 0.3</td>
<td>1.4 ± 0.2</td>
<td>0.11&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>109 1.3 ± 0.3</td>
<td>42 1.3 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>0.09&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>109 1.0 (0.9 - 1.3)</td>
<td>42 1.1 (1.0 - 1.3)</td>
<td>0.5 (0.5 - 0.6)</td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>109 0.80 (0.67 - 1.00)</td>
<td>42 0.85 (0.69 - 1.08)</td>
<td>0.38 (0.33 - 0.46)</td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>112 0.8 (0.6 - 1.0)</td>
<td>43 0.9 (0.7 - 1.0)</td>
<td>0.7 (0.5 - 1.0)</td>
<td>0.16&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>100 263 (123 - 514)</td>
<td>36 221 (109 - 500)</td>
<td>100 (100 - 247)</td>
<td>0.11&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>101 0.6 (0.6 - 1.0)</td>
<td>36 0.6 (0.6 - 0.6)</td>
<td>0.6 (0.6 - 0.6)</td>
<td>0.51&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are given as median (Q1 - Q3), n (%) or mean ± SD.

<sup>1</sup>p-values from FH(11-15) versus NonFH
<sup>2</sup>Chi-square test for independence
<sup>3</sup>Mann-Whitney U test
<sup>4</sup>Independent samples t-test

FH = familial hypercholesterolemia; FH (age 11-15) = FH subjects aged 11-15 years at completion of SmartDiet questionnaire; Non-FH = Non-FH children; CRP = C-reactive protein
Table 3. Characteristics and comparison of FH subjects receiving/not receiving statin treatment.

<table>
<thead>
<tr>
<th></th>
<th>FH + statin (n=66)</th>
<th>FH statin (n=46)</th>
<th>p (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.7 ± 4.1</td>
<td>18.3 ± 5.2</td>
<td>&lt;0.001 (^2)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (56.1%)</td>
<td>28 (60.9%)</td>
<td>0.75 (^3)</td>
</tr>
<tr>
<td><strong>Drug treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other lipid lowering drugs</td>
<td>0 (0.0%)</td>
<td>4 (8.7%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthomas</td>
<td>0 (0.0%)</td>
<td>2 (4.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Xanthelasms</td>
<td>0 (0.0%)</td>
<td>1 (2.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Arcus cornea</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Tendinittis</td>
<td>0 (0.0%)</td>
<td>3 (7.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Thickened heal tendons</td>
<td>0 (0.0%)</td>
<td>2 (4.7%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>7.1 ± 1.5</td>
<td>5.3 ± 0.8</td>
<td>&lt;0.001 (^2)</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>5.4 (4.1 - 5.9)</td>
<td>3.3 (3.0 - 3.7)</td>
<td>&lt;0.001 (^4)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>1.3 (1.2 - 1.6)</td>
<td>1.3 (1.2 - 1.5)</td>
<td>0.91 (^4)</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>1.3 (1.2 - 1.5)</td>
<td>1.3 (1.2 - 1.5)</td>
<td>0.53 (^4)</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>1.2 (1.0 - 1.4)</td>
<td>1.0 (0.9 - 1.0)</td>
<td>&lt;0.001 (^4)</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>0.92 (0.75 - 1.08)</td>
<td>0.69 (0.57 - 0.85)</td>
<td>&lt;0.001 (^4)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.8 (0.6 - 1.0)</td>
<td>0.8 (0.6 - 1.0)</td>
<td>0.80 (^4)</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>223 (105 - 380)</td>
<td>328 (152 - 580)</td>
<td>0.12 (^4)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.6 (0.6 - 1.2)</td>
<td>0.6 (0.6 - 1.2)</td>
<td>0.58 (^4)</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD, n (%), or median (Q1 - Q3)

n indicates number of individuals

\(^1\) p: FH subjects not receiving statin treatment versus FH subjects receiving statin treatment

\(^2\) Independent samples t-test

\(^3\) Chi-square test for independence

\(^4\) Mann-Whitney U test

FH = familial hypercholesterolemia; FH + statin = FH subjects that are not statin treated; FH statin = FH subjects that are statin treated; CRP = C-reactive protein
4.1.2 SmartDiet scores in FH-children and non-FH children

SmartDiet scores were obtained from 100 FH subjects, 39 FH subjects in the age of 11-15 years and 27 non-FH children. The median levels of the SmartDiet scores in each group are shown in table 4. The values differed significantly, p < 0.001, between the FH children aged 11-15 years and the non-FH children, with the FH-children achieving the highest scores. Both groups had median scores within the middle score group (28-35 points).

Table 4. SmartDiet scores of the total FH group, FH children aged 11-15 and non-FH children, with comparison between FH children aged 11-15 years and non-FH children

<table>
<thead>
<tr>
<th></th>
<th>All FH subjects (n = 112)</th>
<th>FH (11-15) (n = 43)</th>
<th>Non-FH (n = 29)</th>
<th>p¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmartDiet score</td>
<td>100 32.0 (30.0 - 34.0)</td>
<td>39 31.0 (30.0 - 34.0)</td>
<td>27 28.0 (25.5 - 29.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are given as median (Q1 - Q3)

n indicates number of individuals.

¹p-values from SmartDiet scores of FH children aged 11 to 15 years versus non-FH children, tested with Mann-Whitney U test

FH = Familial hypercholesterolemia; FH (11-15) = FH children aged 11-15 years; Non-FH = non-FH children (age; 13 years)

4.1.3 Food frequencies among FH children and non-FH children

Table 5a and table 5b show which foods among the different categories that were most frequently consumed by the FH subjects as a whole group, the FH subjects aged 11 to 15 years, and the non-FH children, with statistical comparison between the two last mentioned groups.

Important sources of dietary fatty acids and cholesterol

Significant differences were observed regarding use of different milk types between the FH-children aged 11-15 years and the non-FH children (p<0.001) (table 5a). Of the FH children aged 11 to 15 years, 64.3% used skimmed milk most often, and 23.8% used low-fat milk the most. The results were similar to the entire FH group (66.7% and 24.1%). The opposite pattern was observed for the non-FH children, where 17.9% used skimmed milk and 60.7%
used low-fat milk. None of the FH subjects used whole fat milk, while 7.1% of the healthy children used this type of milk most often.

The use of cheese also differed significantly between the two groups of children (p<0.001) (table 5a). The majority of children from the total FH group used cheese more than once a week (89.3%). The distribution among low-, medium and whole fat cheese was quite even in both the entire FH group and among the FH children aged 11-15, with an approximation of 30% using each category most frequently. Among the non-FH children, the majority (75.9%) used whole fat cheese most often, and 10.3% used medium fat cheese, while only 3.4% (1 subject) used low fat cheese. Out of the 29 non-FH children, 3 subjects (10.3%) did not use cheese more than once a week, while among the FH-children aged 11-15, 2 subjects (5.3%) out of the 38 reported that their cheese intake did not exceed once a week.

Concerning meat as cold cuts on bread (table 5a), the majority of the FH-children aged 11-15 years (73.2%) used lean meat most often, while the use of lean and fat meat as cold cuts was distributed equally among the non-FH children. The proportions that used the different types of meat as cold cuts differed significantly between the FH-children and the non-FH subjects (p=0.004). The share of subjects that had meat as cold cuts on bread once a week or less was small in both FH groups and among the non-FH children.

Regarding the most often used types of meat for dinner, significant differences were observed (p=0.001) (table 5a). Lean types were the most frequent in both FH subjects and non-FH subjects. However, none of the FH-children aged 11-15 years used high-fat cuts, while 24% of the non-FH children used high-fat cuts most frequently. Ten % of the FH children aged 11-15 years used medium-fat cuts, a share that was quite similar to the percentage of non-FH children that used medium-fat cuts most often. The rest of the FH-children aged 11-15 years (90%) used lean cuts most frequently. All the children in the last mentioned group had meat for dinner more than once a week, while one subject among the non-FH children had meat for dinner only once a week or less.

No significant difference regarding reported egg consumption was observed between the two groups. Median use in both groups was two eggs a week (table 5a).

Among the FH children aged 11-15, 74 % reported that they most often used margarine with highly unsaturated fatty acids on bread, very distinct to the 14 % among the non-FH children.
The most frequently reported alternative among the non-FH children was use of hard margarine. In both groups, quite similar shares (19% and 24% respectively) reported that they usually did not use fat on bread (table 5a). The proportions of FH children and non-FH children that used the different types of margarine or butter differed significantly (p<0.001).
Table 5a. Frequency table showing which food items among categories of foods that are chosen most frequently in FH subjects and non-FH children, with comparison of FH subjects aged 11-15 years and non-FH children (13 years old).

<table>
<thead>
<tr>
<th>Food Item</th>
<th>All FH subjects (n=112)</th>
<th>FH (11-15) (n=43)</th>
<th>Non-FH (n=29)</th>
<th>p&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>≤ 1 litre per week</td>
<td>108</td>
<td>42</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Whole fat</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Low-fat milk</td>
<td>26 (24.1%)</td>
<td>10 (23.8%)</td>
<td>17 (60.7%)</td>
<td></td>
</tr>
<tr>
<td>Skimmed</td>
<td>72 (66.7%)</td>
<td>27 (64.3%)</td>
<td>5 (17.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cheese</strong></td>
<td>103</td>
<td>38</td>
<td>29</td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>≤ once a week</td>
<td>11 (10.7%)</td>
<td>2 (5.3%)</td>
<td>3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Whole fat cheese</td>
<td>29 (27.2%)</td>
<td>11 (26.9%)</td>
<td>22 (75.9%)</td>
<td></td>
</tr>
<tr>
<td>Medium-fat cheese</td>
<td>35 (34.0%)</td>
<td>12 (31.6%)</td>
<td>3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Low-fat cheese</td>
<td>29 (28.2%)</td>
<td>13 (34.2%)</td>
<td>1 (3.4 %)</td>
<td></td>
</tr>
<tr>
<td><strong>Meat as cold cuts</strong></td>
<td>107</td>
<td>41</td>
<td>28</td>
<td>0.004&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>≤ once a week</td>
<td>13 (12.1%)</td>
<td>3 (7.3%)</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Fat meat</td>
<td>17 (15.9%)</td>
<td>8 (19.5%)</td>
<td>12 (42.9 %)</td>
<td></td>
</tr>
<tr>
<td>Lean meat (&lt;10 % fat)*</td>
<td>77 (72%)</td>
<td>30 (73.2 %)</td>
<td>12 (42.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Meat for dinner</strong></td>
<td>107</td>
<td>40</td>
<td>29</td>
<td>0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>≤ once a week</td>
<td>3 (2.8%)</td>
<td>0 (0%)</td>
<td>1 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>High-fat cuts</td>
<td>3 (2.8%)</td>
<td>0 (0%)</td>
<td>7 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>Medium-fat cuts</td>
<td>10 (9.3%)</td>
<td>4 (10%)</td>
<td>4 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Lean cuts</td>
<td>91 (85%)</td>
<td>36 (90%)</td>
<td>17 (58.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Eggs per week</strong></td>
<td>107</td>
<td>43</td>
<td>27</td>
<td>0.38&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 (1.0 - 2.25)</td>
<td>2 (1.0 - 2.75)</td>
<td>2 (1.5 - 3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Butter and margarine on bread</strong></td>
<td>110</td>
<td>42</td>
<td>29</td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Usually no butter or margarine</td>
<td>28 (25.5%)</td>
<td>8 (19%)</td>
<td>7 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>Butter/hard margarine</td>
<td>3 (2.7%)</td>
<td>0 (0%)</td>
<td>13 (44.8%)</td>
<td></td>
</tr>
<tr>
<td>Soft margarine</td>
<td>4 (3.6%)</td>
<td>3 (7.1%)</td>
<td>5 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>Margarine with highly unsaturated fat</td>
<td>75 (68.2%)</td>
<td>31 (73.8%)</td>
<td>4 (13.8%)</td>
<td></td>
</tr>
</tbody>
</table>

n indicates number of individuals

<sup>1</sup>p-values from comparison of FH children aged 11 to 15 years old and non-FH children

<sup>2</sup>Fisher's exact test

<sup>3</sup>Mann-Whitney U test

*Oil based patés in this cathegory contains ~20% fat, but highly unsaturated

FH = familial hypercholesterolaemia; FH (11-15) = FH subjects aged 11 to 15 years old; Non-FH = non-FH children
Table 5b. Frequency table showing which food items among categories of foods that are chosen most frequently in FH subjects and non-FH children, with comparison of FH children aged 11-15 years and non-FH children (13 years old)

<table>
<thead>
<tr>
<th></th>
<th>FH All FH subjects (n=112)</th>
<th>FH (11-15) (n=43)</th>
<th>Non-FH (n=29)</th>
<th>p1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fish on bread</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One slice a week or less</td>
<td>109</td>
<td>43</td>
<td>28</td>
<td>0.082</td>
</tr>
<tr>
<td>On two or more slices a week</td>
<td>41 (37.6%)</td>
<td>14 (32.6%)</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fish for dinner</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a week or less</td>
<td>111</td>
<td>43</td>
<td>29</td>
<td>0.292</td>
</tr>
<tr>
<td>Two times a week or more</td>
<td>41 (36.9%)</td>
<td>14 (32.6%)</td>
<td>13 (44.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Omega-3 supplements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not use supplement containing omega-3</td>
<td>109</td>
<td>42</td>
<td>25</td>
<td>0.632</td>
</tr>
<tr>
<td>Uses supplement containing omega-3</td>
<td>63 (57.8%)</td>
<td>26 (61.9%)</td>
<td>14 (56.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Bread type/grain products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not eat bread/grain products</td>
<td>108</td>
<td>41</td>
<td>28</td>
<td>0.683</td>
</tr>
<tr>
<td>Low in fiber</td>
<td>30 (27.8%)</td>
<td>17 (41.5%)</td>
<td>9 (32.1%)</td>
<td></td>
</tr>
<tr>
<td>High in fiber</td>
<td>76 (70.4%)</td>
<td>23 (56.1%)</td>
<td>19 (67.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Vegetables/fruits/berries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than two portions a day</td>
<td>106</td>
<td>42</td>
<td>29</td>
<td>0.233</td>
</tr>
<tr>
<td>Two or more portions a day</td>
<td>68 (64.2%)</td>
<td>29 (69.0%)</td>
<td>16 (55.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Plant sterols</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not use a product containing plant sterols</td>
<td>105</td>
<td>41</td>
<td>27</td>
<td>&lt;0.0012</td>
</tr>
<tr>
<td>Uses a product containing plant sterols</td>
<td>58 (55.2%)</td>
<td>19 (46.3%)</td>
<td>26 (96.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sweet spreads or sweet drinks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than two times a day</td>
<td>108</td>
<td>41</td>
<td>28</td>
<td>0.042</td>
</tr>
<tr>
<td>Two or more times a day</td>
<td>72 (66.7%)</td>
<td>22 (53.7%)</td>
<td>22 (78.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Snacks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than two times a week</td>
<td>109</td>
<td>41</td>
<td>29</td>
<td>0.142</td>
</tr>
<tr>
<td>Two or more times a week</td>
<td>71 (65.1%)</td>
<td>31 (75.6%)</td>
<td>26 (89.7%)</td>
<td></td>
</tr>
</tbody>
</table>

n indicates number of individuals

1p-values from comparison of FH children aged 11 to 15 years old and non-FH children

2Chi-square test for independence

3Fisher’s exact test

FH = familial hypercholesterolaemia; FH (age 11-15) = FH children aged 11 to 15 years old; Non-FH = non-FH children
**Fish and omega-3 dietary supplements**

Neither the use of fish on bread or fish for dinner was reported differed significantly between the FH children of 11-15 years and the non-FH children, as shown in table 5b. In both groups, most children reported that they used fish on bread or in salads once a week or less. However, in both groups, most children also reported that they had fish for dinner two times a week or more. No significant differences were observed between the two compared groups of children regarding use of omega-3 supplements. In both groups, about 40% reported that they did not use this form of supplement. The use of fish among the FH children aged 11-15 was very similar to that of the entire FH group.

**Important sources of fiber and plant sterols**

Similarity between the FH children aged 11-15 and the non-FH children was observed regarding reported types of bread and grain products most frequently used. In both groups, the majority reported most frequent use of the options more rich in fiber, although using bread types lower in fiber most often was also reported frequently in both groups (41.5 % of the FH children aged 11-15 and 32.1 % of the non-FH children). Among the total group of FH subjects, use of bread rich in fiber was more frequent than in the subgroup of FH children.

In the case of vegetables, fruits and berries, more than half of the FH children aged 11-15 and of the non-FH children reported that they had 2 or more portions a day. Meanwhile, 31 % and 44.8 % reported that they had less than 2 portions a day, respectively. No significant difference observed between the two groups. The reported intakes in the sub-group of FH children were similar to those of the total group of FH subjects.

More than half of the FH children aged 11-15 years used a product containing plant sterols. Among the non-FH children, one subject reported use of such a product (p < 0.001).

**Sources of added sugar**

No significant differences were observed regarding use of snacks between the two groups of children. There was a significant difference in use of sweet spreads and drinks, with the greater proportion of non-FH children reporting daily use as less than two times (p=0.04).
4.2 Lipid levels and SmartDiet scores

No statistical significant correlations were observed when correlations between SmartDiet scores, blood lipid levels and CRP were investigated in the total FH group or in the group of FH subjects aged 11-15 years (table 6). In the group of non-FH children, triglycerides and SmartDiet scores showed a statistically significant inverse correlation coefficient of -0.38 (p=0.048). All other correlation coefficients were non-significant.

To investigate if statin treatment possibly disturbed any correlations the group was split into those who were statin treated and those who were not. No statistically significant correlations were observed in either group of FH subjects. Results are shown in table 7.
Table 6. Spearman's rank correlation coefficient between SmartDiet scores and lipid levels and CRP in FH subjects, FH subjects aged 11-15 years and non-FH children (13 years old)

<table>
<thead>
<tr>
<th></th>
<th>FH (n=100)</th>
<th>FH (11-15) (n=39)</th>
<th>Non-FH (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>n</td>
<td>rₛ</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>-0.04</td>
<td>0.71</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>99</td>
<td>-0.03</td>
<td>0.81</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>100</td>
<td>0.003</td>
<td>0.98</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>97</td>
<td>0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>97</td>
<td>-0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>97</td>
<td>-0.02</td>
<td>0.84</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>100</td>
<td>-0.01</td>
<td>0.94</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>90</td>
<td>0.09</td>
<td>0.39</td>
</tr>
</tbody>
</table>

n indicates number of individuals
rₛ = Spearman's rank correlation coefficient between SmartDiet score and laboratory parameter
p-values from Spearman's rank correlation
FH = familial hypercholesterolemia; FH (11-15) = FH subjects aged 11-15 years at completion of SmartDiet questionnaire; Non-FH = Non-FH children; CRP = C-reactive protein
Table 7. Spearman’s rank correlation coefficient between SmartDiet scores and lipid levels and CRP in FH-subjects who are statin treated and FH-subjects who are not statin treated.

<table>
<thead>
<tr>
<th></th>
<th>FH + statin (n=57)</th>
<th></th>
<th>FH statin (n=43)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>rs</td>
<td>p</td>
<td>n</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>57</td>
<td>0.04</td>
<td>0.76</td>
<td>43</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>56</td>
<td>0.05</td>
<td>0.72</td>
<td>43</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>57</td>
<td>-0.05</td>
<td>0.85</td>
<td>43</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>56</td>
<td>0.02</td>
<td>0.88</td>
<td>41</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>56</td>
<td>0.11</td>
<td>0.41</td>
<td>41</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>56</td>
<td>0.07</td>
<td>0.62</td>
<td>41</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>57</td>
<td>-0.11</td>
<td>0.41</td>
<td>43</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>53</td>
<td>0.03</td>
<td>0.85</td>
<td>37</td>
</tr>
</tbody>
</table>

n indicates number of individuals

rs=Spearman's rank correlation coefficient between SmartDiet scores and laboratory parameter values

p-values from Spearman's rank correlation

FH = familial hypercholesterolemia; FH + statin = FH subjects that are not statin treated;

FH statin = FH subjects that are statin treated

4.3 Inheritance of FH from mother or father

Sixty-three of the FH subjects had inherited the disorder from their mother and 48 had it from their father. One child was adopted with no information on inheritance retrievable in the medical record.

4.3.1 SmartDiet scores

Results from the investigation of SmartDiet scores of those who inherited the disease from their mother and those who inherited it from their father are shown in table 8. No significant difference was observed.
4.3.2 Lipid values and CRP

The total FH group

In table 8 characterizations of subjects who inherited FH from their mother and from their father are shown, respectively.

Table 8. Comparison of the SmartDiet scores and the lipid values between children and young adults with maternal- and paternal FH

|                        | FH from mother (n=63) | FH from father (n=48) | p
|------------------------|-----------------------|-----------------------|---
| n                      | 63                    | 48                    | 0.29
| Age (years)            | 56 15.0 (12.5 - 18.0) | 43 16.0 (12.0 - 19.5) | 0.09
| Female                 | 63 32 (50.8%)         | 48 32 (66.7%)         | 0.57
| SmartDiet score        | 56 33.0 (30.00 - 34.00) | 43 32.0 (29.75 - 33.50) | 0.17
| Statin treated         | 63 22 (34.9%)         | 48 23 (47.9%)         | 0.28
| Total cholesterol (mmol/L) | 63 6.3 (5.3 - 7.8) | 48 5.9 (5.1 - 7.5) | 0.26
| Low density lipoprotein cholesterol (mmol/L) | 62 4.2 (3.3 - 5.6) | 48 3.9 (3.2 - 5.5) | 0.23
| High density lipoprotein cholesterol (mmol/L) | 63 1.3 (1.1 - 1.5) | 48 1.4 (1.2 - 1.6) | 0.09
| Apolipoprotein A1 (g/L) | 62 1.3 (1.1 - 1.5) | 46 1.3 (1.2 - 1.5) | 0.37
| Apolipoprotein B (g/L) | 62 1.0 (0.9 - 1.3) | 46 1.0 (0.9 - 1.3) | 0.07
| Apolipoprotein B/Apolipoprotein A1 | 62 0.82 (0.69 - 1.00) | 46 0.72 (0.59 - 1.00) | 0.73
| Triglycerides (mmol/L) | 63 0.9 (0.6 - 1.1) | 48 0.7 (0.5 - 1.0) | 0.47
| Lipoprotein (a) (mg/L) | 57 220 (117 - 490) | 42 282 (135 - 552) | 0.73
| CRP (mg/L)             | 59 0.6 (0.6 - 1.0) | 41 0.6 (0.6 - 1.0) | 0.47

Data are given as median (Q1 - Q3) or n (%)

n indicates number of individuals

1 p-values from FH from mother versus FH from father

2 Mann-Whitney U test

3 Chi-square test for independence

FH = familial hypercholesterolemia; FH from mother = FH subjects who inherited FH from their mother; FH from father = FH subjects who inherited FH from their father; CRP = C-reactive protein

42
No significant values were observed regarding any of the laboratory parameters in the initial analyses. However, there was a tendency towards significance in apo A1 (p=0.09), apo B/apo A1 ratio (p=0.07) and triglyceride values (p=0.07), with those who inherited FH from their father having lower values. In the case of Lp(a) the data material contained extreme values. When these were removed, differences in Lp(a) remained non-significant.

In addition, we investigated whether there was a difference in the proportion of subjects with Lp (a) values > 300 mg / L in those who had inherited FH from their father compared with those who had inherited FH from their mother. Forty-eight % of those who had FH from their father and 40% of those who had FH from their mother had Lp(a) values above 300 mg/L. The difference was non-significant.

**FH subjects without statin treatment**

To investigate whether statin treatment possibly masked any effect of inheritance on lipid values and inflammatory markers, similar analyses were performed solely on those who were not statin treated, who were 65 % of the subjects that had FH from their mother and 52 % of those whose father had FH. The results are shown in table 9. No significant differences were observed between the two groups.

CRP was also categorized into CRP values <1 mg/L, 1-3 mg/L and >3 mg/L in these subjects in an additional analysis (data not shown). Still no significant differences in CRP levels were observed between the two groups.
Table 9. Comparison of the SmartDiet scores and the lipid values between children and young with maternal- and paternal FH that are not statin treated

<table>
<thead>
<tr>
<th></th>
<th>FH from mother (n = 41)</th>
<th>FH from father (n = 25)</th>
<th>p1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 14 (12 - 15)</td>
<td>22 14 (10 - 18)</td>
<td>0.82</td>
</tr>
<tr>
<td>Female</td>
<td>41 21 (51.2%)</td>
<td>25 16 (64.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>SmartDiet score</td>
<td>35 33 (30 - 34)</td>
<td>22 32 (30 - 33)</td>
<td>0.91</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>41 7.1 ± 1.6</td>
<td>25 7.1 ± 1.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>40 5.1 ± 1.3</td>
<td>25 5.2 ± 1.2</td>
<td>0.69</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>41 1.4 (1.1 - 1.6)</td>
<td>25 1.3 (1.2 - 1.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>41 1.3 (1.1 - 1.5)</td>
<td>24 1.3 (1.2 - 1.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>41 1.2 (1.0 - 1.4)</td>
<td>24 1.3 (1.1 - 1.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>41 0.86 (0.75 - 1.08)</td>
<td>24 0.92 (0.77 - 1.13)</td>
<td>0.74</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>41 0.9 (0.6 - 1.1)</td>
<td>25 0.7 (0.5 - 1.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>36 185 (100 - 501)</td>
<td>22 258 (135 - 321)</td>
<td>0.89</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>40 0.6 (0.6 - 1.0)</td>
<td>21 0.6 (0.6 - 1.0)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Data are given as median (Q1 - Q3), n (%) or mean ± SD
n indicates number of individuals
1p-values from FH inherited from mother vs FH inherited from father
2Mann-Whitney U test
3Chi-square test for independence
4Independent samples t-test
FH = familial hypercholesterolemia; FH from mother = FH subjects who inherited FH from their mother;
FH from father = FH subjects who inherited FH from their father; CRP = C-reactive protein

FH subjects receiving statin treatment

Thirty-five % of those who had inherited FH from their mother and 48 % of those who had it from their father were statin-treated. Characteristics are shown in table 10. The apo B/apo A1 ratio was significantly lower in those who had inherited the disease from their father (p=0.001). No other significant differences were seen, although a tendency towards significant lower values in those who had inherited FH from their father was observed in HDL-C (p=0.06), apo A1 (p=0.08) and apo B (p=0.07).
Table 10. Comparison of the SmartDiet scores and the lipid values between children and young with maternal- and paternal FH that are not statin treated

<table>
<thead>
<tr>
<th></th>
<th>FH from mother (n = 22)</th>
<th>FH from father (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>23</td>
<td>0.18</td>
</tr>
<tr>
<td>Age on date of SmartDiet completion</td>
<td>21 (18.0 (14.0 - 21.0))</td>
<td>21 (19.0 (15.0 - 23.0))</td>
<td>0.75</td>
</tr>
<tr>
<td>SmartDiet score</td>
<td>21 (33 (30 - 34))</td>
<td>21 (32 (29.5 - 34.0))</td>
<td>0.55</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>22 (5.3 (4.9 - 5.7))</td>
<td>23 (5.2 (4.5 - 5.5))</td>
<td>0.35</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mmol/L)</td>
<td>22 (3.6 (3.0 - 4.0))</td>
<td>23 (3.2 (2.7 - 3.7))</td>
<td>0.12</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>22 (1.3 (1.1 - 1.4))</td>
<td>23 (1.5 (1.3 - 1.7))</td>
<td>0.06</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>21 (1.3 (1.1 - 1.4))</td>
<td>22 (1.4 (1.3 - 1.5))</td>
<td>0.08</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>21 (1.0 (0.9 - 1.1))</td>
<td>22 (0.9 (0.7 - 1.0))</td>
<td>0.07</td>
</tr>
<tr>
<td>Apolipoprotein B/Apolipoprotein A1</td>
<td>21 (0.77 (0.67 - 0.91))</td>
<td>22 (0.61 (0.53 - 0.69))</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>22 (0.9 (0.6 - 1.1))</td>
<td>23 (0.7 (0.5 - 0.9))</td>
<td>0.25</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/L)</td>
<td>21 (284 (153 - 449))</td>
<td>20 (378 (124 - 699))</td>
<td>0.58</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>19 (0.6 (0.6 - 1.3))</td>
<td>20 (0.9 (0.6 - 1.2))</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Data are given as n(%) or median (Q1 - Q3)

*n* indicates number of individuals

1*p*-values from FH inherited from mother versus FH inherited from father

2Chi-square test for independence

3Mann-Whitney U test

*remains significant (p = 0.01) when extreme value is removed

FH = familial hypercholesterolemia; FH from mother = FH subjects who inherited FH from their mother; FH from father = FH subjects who inherited FH from their father; CRP = C-reactive protein
5 Discussion

5.1 Discussion of subjects and methods

5.1.1 Study design

This study is part of a larger project conducted on a cohort of FH children, investigating
importance of family history (e.g. type of mutation, premature disease) and identifying early
atherosclerotic markers. The Lipid Clinic is an outpatient clinic with national responsibility
for the treatment and follow-up of children with FH. Hundred to 150 children are followed up
annually. The dietary registration questionnaire (SmartDiet) was mailed to all children (5-18
years) who had been at the outpatient clinic in the period 2000-2010. However, in order to
avoid an actual visit at the Lipid Clinic (trying to include as many children as possible and
from the whole of Norway), and based on the information that children with FH are annually
followed-up, it was decided to use biochemical data available from the medical journals at the
Lipid Clinic.

By using this design we were able to collect much information simultaneously and thus able
to investigate relations between several variables. Besides, information was only required
from the participants once, which was less demanding on them.

In order to be able to compare the dietary registration and the food choices with a reference
population, we decided to include a group of non-FH children. Previous experience have
shown that it is very difficult to recruit non-FH children for these kind of studies, so it was
decided to take advantage of the fact that two school classes were recruited in the study in
relation to the main project.

5.1.2 Subjects

Our study sample included FH-subjects aged 5 to 28 years, an age range that implies that the
subjects are a quite heterogeneous group. With this heterogeneous group, difficulties may
arise on generalizing results to FH subjects in more narrow age groups. We decided to extract
a group that could represent FH children from middle school and late primary school that was
also considered comparable to the group of non-FH children. All the non-FH children were
Caucasians as were almost all the FH children. However, while the FH subjects came from all over Norway, the non-FH children were all recruited from the same school at Nordstrand in Oslo, and from the same grade. This might have caused the non-FH children to constitute a more homogenous group than the FH children, with respect to factors such as socioeconomic status (SES), neighborhood and food environment, possibly lessening the degree of comparability with the FH group. In addition, the non-FH children were all the same age, but were compared to FH subjects with an age range of four years.

The gender distribution was evenly distributed in the total FH-group and the subgroup of FH subjects, resembling children and young FH patients in general. The similarities regarding all variables between the whole FH group and the subgroup of FH children suggest that we might have been able to compare the non-FH group and the entire group of FH subjects. In both FH groups, the number of subjects receiving statin therapy and subjects free of lipid-lowering medications were sufficient to make analyses on both groups regarding lipid levels and their relation to diet and parental history. One hundred and twelve children and young FH subjects may also be considered a relatively large sample size, as they are recruited from the Norwegian population which may be considered quite homogeneous.

However, only about 30 % of the invited FH-patients responded to the invitation. The loss of about 70 % of invited subjects and in addition the subjects that were excluded due to missing parts in the responses, may have introduced selection bias in the sample. We do not know if those who did not respond share common features that are different from those who responded. Indeed, adolescents abstaining from participating in health studies have been associated with certain characteristics, as listed by Bjertness et al [125]. A less favorable lifestyle is one of the traits [126], and it is not impossible that this would also include less attention towards dietary recommendations. Certain parental features such as low maternal income or education may also influence participation in health studies [125]. Income and education are both factors that have been associated with dietary patterns [127, 128]. Additionally, the SmartDiet questionnaire lists many typical Norwegian food items and may be less suitable and less appealing to people from other food cultures. An investigation of the geographical distribution of the FH subjects also revealed that most were from the southern part of Norway, with the majority living in the south-east. The possibility that groups of FH patients with certain common characteristics have not been incorporated in the study could make the results less representative of children and young FH patients as a whole.
5.1.3 Registration of diet and food choices

Response bias

One disadvantage common to all dietary assessment methods is that subjects may report what they expect to be a “healthier” diet than usually consumed, attempting to impress or to avoid criticism [71]. As the FH-subjects constitute a group of patients that receives dietary treatment, it is not unreasonable to assume that they perceive certain expectations concerning what they are supposed to eat, and possibly turn their answers in direction of these expectations.

The SmartDiet questionnaire as tool for dietary registration

The SmartDiet questionnaire may be considered easy and little time-consuming to complete. As the questionnaire is familiar to the FH subjects, the risk of misunderstandings should also be reduced. Using a self-administered questionnaire to measure usual diet is also time-saving to the researcher as subjects completes the questionnaire on their own. Besides one avoids the risk of asking “leading questions” that may occur in an interview setting. The answers are also more easily standardized in the data assessment than answers from an interview.

Regarding information on amount of certain food components in diet, the SmartDiet questionnaire validation study indicated that the questionnaire may provide good estimates of dietary fat and fiber. These are both dietary components that have been associated with cholesterol levels [60, 129].

The SmartDiet questionnaire may however not give a fully representative picture of intakes of the dietary components that are included in the form. The validation study showed less strong agreement rates with dietary intakes of snacks, fish and vegetables and fruits [124]. The latter seems to be a frequent limitation of food questionnaires, as low validity in children’s reported intakes of fruits and vegetables is a reported finding in validation studies [130]. This possibly indicates that children have difficulties of recalling and estimating their habitual intakes of this type of food, which may imply that FFQ’s and resembling questionnaires are unsuitable for measuring children’s usual intakes of vegetables and fruit.

Another limitation regarding validity of the SmartDiet questionnaire is that the current questionnaire and the use of the questionnaire on the present study sample may have been
incompletely evaluated. The validation study on the SmartDiet questionnaire was performed before the two revisions of the form were carried out [123, 124]. Besides, the validation study was performed on subjects above 18 years of age [124], while in the present study children and adolescents constitute the majority of subjects. However, most likely in the present study, parents have filled out or at least helped filling out the questionnaires in many cases.

The SmartDiet questionnaire has been used prior to all clinical consultations at the Lipid Clinic since 2004 [123]. It is reasonable to presume that the FH subjects or at least their parents were already familiar with this questionnaire. The FH subjects or their parents have also been to consultations where their responses have been discussed with clinicians, a situation that may correct misunderstandings and cause more reliable responses in later completions. The non-FH children, and their parents if they were helping, probably completed the questionnaire for their first time and without ever being offered the previously mentioned guidance opportunity. As a result, the responses from the non-FH children may to a greater extent have been influenced by misunderstandings. There is a possibility that the difference in familiarity with the SmartDiet questionnaire might have caused differential misclassification regarding choices of food items between non-FH children and FH children aged 11-15 years old. However, in the validation study of the SmartDiet questionnaire, 90% of participants found the questionnaire easy or very easy to understand, suggesting the risk of misunderstandings might not be that disturbing.

**Parents as surrogates for children**

It is unlikely that the youngest subjects in this study completed the SmartDiet questionnaire on their own. Parents have probably acted as surrogates for many of the children in the dietary assessment. As children may be unfamiliar with many food items, and may not yet have developed an accurate ability to recall details from the past, parents that act as surrogates may be the better option in dietary assessment in young children. However, parents may be well aware of what is eaten during meals, but less aware of what is eaten between meals [131]. Thus, misreporting from parents cannot be excluded. However, what is eaten outside meals may be of less importance in this study, as meal time intakes probably constitute most of the diet. Furthermore, the most frequent food items between meals are probably snacks and fruits, and not major fat sources influencing the cholesterol level.
5.1.4 Clinical data from medical records

Medical records are likely to be reliable sources of data regarding the subjects’ use of lipid lowering medications and parental FH, as these are aspects that are important parts of FH treatment and of the mapping of potential other carriers of FH mutations. However, medical records may be subject to recall bias by the physician, possibly causing incorrect information. Another drawback by using medical records is that they do not follow a standardized format, meaning information of interest may be missing in many journals, as was the case in this study where we were unable to investigate certain parameters of interest due to inconsistent reports on these parameters in the medical records. However, by using information already gathered in the medical records, time and resources are saved. The method is cheap and less demanding for the study participants.

5.1.5 Laboratory parameters

The majority of blood samples were analyzed at the same laboratory, suggesting methodological differences were not of much impact regarding results, although some influence of methodological discrepancies cannot be excluded. All laboratory parameters except Lp(a) and CRP were obtainable from more than 97% of participants, so that missing values was not a problem in the case of most parameters.

The Lp(a) values were in many cases measured at a different point in time, compared to the rest of the laboratory parameters. However, Lp(a) is a parameter primarily genetically determined and not influenced by many factors [44]. Some values were measured more than a decade ago and in different laboratories, so there is a risk that methodically differences reduce the comparability of the measured values, as there is no standardized method for measuring Lp(a) [44]. However, one can assume that risk of misclassification in terms of reference value is small, as Lp(a) values dispose wide variety in the population in general[44]. High levels of Lp(a) are often much higher than the reference value of 300 mg/L. Accordingly, eventual measurement errors are unlikely to affect the perception of the Lp(a) level in terms of CVD risk. This is because the measurement error is unlikely to override the actual difference between the real level of Lp(a) and the reference value. Risk of misclassification is thus only a problem when the reference value and the measured value are close to one another.
**Time of blood sampling and dietary registration**

Ideally the dietary registration and the blood sampling should have been conducted simultaneously, to exclude any possible changes in diet or blood parameters that might occur meanwhile if the two were conducted at different points in time. Such uncontrollable changes cannot be discounted in this study, as the average time-space between the two measurements was 45 weeks. However, studies have implied that dietary patterns and food choices are fairly stable in the time between adolescence and adulthood, a current époque for many of the FH-subjects [132]. Studies are also suggesting reasonable stability in individual eating pattern from 4th to 7th grade [128] and slight tracking from the age of 9 to 15 years have also been demonstrated [133] although youth may be a period when individuals achieve new dietary habits as well. Concerning cholesterol levels, increases due to adoption of an unhealthy lifestyle from youth to adulthood have been observed [134], and dietary changes have reduced levels in hypercholesterolemic patients within 3 months. The former demonstrates that cholesterol levels may increase, the latter that substantial reductions may also occur in rather short time [135]. However, a recent study of ten years consecutive blood lipid patterns in children aged 8 to 18 years demonstrated significant patterns of only small variations in TC, LDL-C, HDL-C and TG levels with age [136]. The greatest difference in TC and LDL-C levels were observed in boys, where levels were reduced by ~29mg/dl at most (0.75 mmol/L*) between the ages of 9 and 16 years. LDL-C decreased monotonically from ages 8 to 18, with approximately 30 mg/dl (0.78 mmol/L*) in boys, with smaller differences in girls. The HDL-C levels varied with ~20 mg/dl (0.52 mmol/L*) in both genders between the ages of 10 and 16 years. TG levels increased in an almost linear fashion by 45 mg/dl (0.51 mmol/L*) in boys between eight and eighteen years. Smaller increases were observed in girls [136]. Small age related changes in apo A1 and apo B have also been observed, as well as resembling findings regarding changes in TC [137]. The above descriptions of small variations in lipid levels are albeit retrieved from research on normocholesterolemic children, as similar research concerning lipid levels in FH children appears scarce. However, lipid levels may fall in FH affected adolescents as well, as taken into account in the recommendation that FH screening with cholesterol measurements should be performed before adolescence [138]. The cholesterol levels of FH patients might be subject to the same percentage fluctuations as those observed in normocholesterolemic individuals in response to outer influential factors. At least, this has been observed in relation to pregnancy, where FH subjects’ cholesterol levels responded to pregnancy with the same percentage changes as was
observed in normocholesterolemic subjects, relative to the baseline cholesterol levels [139].

Assumingly, lipid levels in children vary over time, but the variations are small, suggesting that any possible relations between the diet and lipid levels as measured by the SmartDiet score and blood analyses would not necessarily be affected by the time space between the two performances. Among those who had more than two years discrepancy, there were only three subjects within the ages of 8-18 years, with one being younger and the rest being older. After puberty lipid levels are more reliable in terms of stability [138].

(*Conversions from mg/dl to mmol/L are performed by means of formulas from ESC/EAS Guidelines for the management of dyslipidemias [18].)

5.1.6 Statistics

In this thesis we used independent samples t-test when the data was normally distributed and Mann-Whitney U test in cases where the data was not normally distributed. The advantage of using the Mann-Whitney U test is that it is less sensitive to outliers than the parametric test. However, non-parametric tests are less powerful than parametric test to detect differences, meaning one could miss statistical significant differences [140]. Independent samples t-test was additionally performed to verify that results were not statistically significant in cases where there was a tendency towards statistical significance.

To analyze potential associations between biochemical parameters and SmartDiet scores we used the non-parametric Spearman’s rank correlation coefficient. This was chosen as it is less sensitive to outliers and as much of the data did not show a normal distribution. However, some of the parameters could have been presented with Pearson’s correlation coefficient, as their data distributions did not violate the assumptions for using this approach. However, after consultation with statistician Marit Veierød, it was decided to use Spearman’s rank order correlation coefficient for all the data. This change in statistical approach and presentation did not affect any statistically significant results, as only minor correlation coefficients and non-significant p-values had been observed with Pearson’s correlation coefficient as well.

Chi-square test was used on 2x2 tables as all met the requirements for the use of such tests. Although Yate’s correction for continuity is recommended with 2x2 tables by some authors [140, 141], we chose not to use this correction, as a recent publication recommends that
Yate’s correction for continuity should no longer be used [142], and the same recommendation was received from consultation with statistician Marit Veierød.

5.2 Results

5.2.1 SmartDiet scores

The comparison of SmartDiet scores in the FH children and the non-FH children showed that the FH children had considerably higher SmartDiet scores than the non-FH children, indicating that FH children have a more healthy diet than children free of FH. The validation study of the questionnaire also supports this interpretation, as a difference of at least 3 points was considered indicative of dietary improvement in that study. Besides, the questionnaire of that time had a broader score range (15-45 points) [124], suggesting that a difference of 3 points constitutes an even greater difference in healthiness of diet in the current questionnaire.

Because heterozygous FH is a disease that affects both the child and a parent, the diet of these children are likely a product of both the parent and the child's diet measures at home. A recent thesis by Fæhn from the University of Oslo looked into the diet of adults with FH and adults with multifactorial hypercholesterolemia, and found that FH subjects had the healthiest diet, supporting the notion that FH patients stand out as a group that is more concerned with their diet [143]. In a study by Tonstad, 154 FH children aged 6-16 years were asked whether they did anything to reduce cholesterol, out of who 88% mentioned the diet as part of their answer [144]. Qualitative studies have also emphasized that FH patients may experience guilt when they do not follow dietary recommendations [145]. Parents' preoccupation to teach their children a healthy lifestyle has also been highlighted [146]. The higher SmartDiet scores of the FH children may reflect that both the children and their FH affected parent have a healthier diet than others.

The comparison of the FH children aged 11-15 and the non-FH children involved comparing a group of children that as a result of treatment had received individual dietary advice at least one time, with children that probably never had been given such guidance. With this in mind, it is reasonable to suggest that the diet counseling has been an influential factor. Since both parents and children are receiving this type of diet counseling, both parents and children's responses to dietary advice may be of importance to the children’s diets. Regardless in whom
the influence is of greatest importance, the higher scores of the FH children might suggest that dietary guidance the way it is offered them through the treatment regimen actually helps to improve their diet.

The SmartDiet scores of the total group of FH subjects were in line with those of the younger FH subjects. The same patterns were also retrievable regarding choices of food. We may assume that the pattern observed is representative of the investigated sample as a whole, regardless of age. Following this assumption, the dietary habits achieved in childhood, at least the degree of healthiness of diet as measured by the SmartDiet questionnaire, seems to be retrievable in early adulthood, when parents might not be as much in charge of what constitutes the usual diet. Observations of dietary consistency from adolescence into adulthood have been found in other studies, suggestive of the beneficial role of implementing healthy dietary habits at an early age, and targeting nutrition education especially at children and adolescents [132].

Although the FH children aged 11-15 years had better SmartDiet scores than the non-FH children, they had, along with the non-FH children, median scores in the middle score group of the SmartDiet questionnaire, which is considered an indication that there are some areas of diet that should be improved to make the diet heart-healthier and generally healthier. The maximum SmartDiet score is 41 points, which is 10 points above the median score of the FH children aged 11-15. This indicates that the diet of FH children is not optimal in terms of healthiness and heart-friendliness, although it might appear healthier than that of other children. The middle score suggests considerable potential of improvement in both groups.

### 5.2.2 Choices of food

The analysis of which food items were most frequently used within the different food categories in the SmartDiet questionnaire implied that the higher SmartDiet scores of the FH-children aged 11-15 stemmed from a systematic pattern of choosing low-fat alternatives, or alternatives high in unsaturated fats. The Norwegian nationwide survey on dietary habits among Norwegian 4th graders and 8th graders (Ungkost-2000) found that meat, dairy products, butter, margarine and oil were the most important sources of fat in the children’s diets, contributing with approximately 50% of dietary fat in both grades [147]. In light of this, as the FH children appear to choose low-fat and highly unsaturated fat alternatives among these foods, it appears that they are choosing favorable alternatives in those areas of diet where
there is the most to gain in order to reduce total fat intake and achieve a favorable fatty acid composition of diet. Their choices of food among these categories were much in contrast with the food choices of the non-FH children, where the use of high fat or medium fat content products was more widespread. Regarding milk and cheese, the division into various options was done by similar means in Ungkost as in the SmartDiet questionnaire, with low fat and whole fat cheese, and the three types of milk. The 8th graders in Ungkost showed a similar pattern as the non-FH children in our study with substantially higher intakes of whole fat cheese and low-fat milk than of the other cheese and milk alternatives, supporting the non-FH group’s representativeness of other children concerning the use of these foods [147]. This further supports that the FH children aged 11-15 are choosing other food options than 13 year olds, regarding some important dietary sources of fat and saturated fatty acids.

There was no difference in the intake of eggs between the FH children aged 11-15 and the non-FH children. On the last page of the SmartDiet questionnaire, a recommendation of no more than two egg yolks a week is given. The FH-children appears to comply with this recommendation. However, as the non-FH children reported similar intake of eggs, this might imply that use of eggs in children’s diets is not that abundant after all, suggesting this recommendation is achievable. However, cautions should be made regarding the exact reported numbers, as the subjects may have experienced difficulties estimating how many eggs they eat per week.

The FH children aged 11-15 years and the non-FH children did not differ significantly in either fish consumption, consumption of vegetables, berries and fruit or in use of fiber rich grain products. This may mean that the FH children are more responsive to dietary advices regarding fat, while dietary advices that might appear less attached to cholesterol levels but serve to make diet healthy in other means, applies to the FH children in quite similar manners as to other children. The intake of fruits and vegetables by Norwegian children have been reported to be low [147-149], compared to the recommended 5 portions per day [150]. The average fruit and vegetable consumption among the FH children aged 11-15 and the non-FH children were not possible to calculate due to the construction of the SmartDiet questionnaire. Nevertheless, about one third of the FH children and almost half of the non-FH children reported daily consumption of less than two portions, suggesting great potential for increase in both groups. Regarding grain products, the majority of both FH children aged 11-15 years and the non-FH children ate grain products high in fiber more frequently than such products.
low in fiber. However, more than 30% in each group reported using low fiber products most frequently. A survey conducted on 7th graders in Telemark county of Norway in 2010 found that more than 20% of the children did not eat whole meal grain products daily [149]. Ungkost-2000 reported that about 30% of 8th graders used white bread [147]. Comparing these data is difficult, as different standards are used. However, there appears to be a potential for improvement in both FH children and Norwegian children in general regarding intakes of grain products high in fiber to improve healthiness of diet.

The similar patterns in FH children aged 11-15 and the non-FH children concerning use of omega-3 dietary supplements might be explained by many different relations. They may imply that recommendations regarding use of such supplements have reached the non-FH children as well, although they have not been to dietary counseling. One possible interpretation is that frequent use of omega-3 dietary supplements among the non-FH children might result from them being a group of children from high SES parents, as their home district is one with high levels of highly educated people [151]. In 2000, Ungkost reported that about 90% of eight-graders never used cod liver oil, and approximately the same percentage did not use cod liver oil capsules at all. Although this was more than ten years ago, and the Ungkost data only included cod liver oil and cod liver oil capsules and no other supplements with omega-3, the discrepancies imply that it would probably be reckless to assume that more than 50% of Norwegian 13 year olds in general now use omega-3 supplements on a regular basis. The finding may also be a result of an imprecise way of posing the question in the SmartDiet questionnaire, as the question does not ask for the frequency of use. In this case, misreporting may apply to both groups of children. Some of those who reported use of such supplements may use this only now and then.

More than 50% of the FH children aged 11-15 reported use of a product containing plant sterols. It appears that recommended use of plant sterols have been accepted by a substantial proportion of the FH children. However, as with omega-3 supplements the question does not imply whether the reported use is on daily basis or of a lower frequency.

As discussed, significant differences in food use were observed in favor of the FH children aged 11-15 having a healthier diet than the group of non-FH children. However, there was observed a significant difference in the use of sweet spreads and sweet drinks that followed an opposite pattern. Avoidance of sugar is not the main target in the dietary treatment of FH, and FH children may therefore be more relaxed on this issue. However, another explanation of
this observation may be that FH children could have higher intakes of sweet spreads such as jam, prim and honey, as these are low in fat and might be chosen instead of spreads as meat and cheese. An investigation of 164 Norwegian FH children in the ages of 6 to 16 years conducted in 1995 found that the children had sucrose intakes of 13-14% of total calories. This is above the recommended levels of <10% of energy intake, and was characterized as high in that study [152]. However, high sugar intakes in Norwegian children was also observed in Ungkost, which reported added sugar to contribute with 18% of total energy intakes in 8th graders [147]. Accordingly, FH-children might not have higher intakes of sugar than other children. However, the possibility that sugared foods replace other types of food in their diet might be noteworthy.

5.2.3 The relations between SmartDiet scores and lipid values

Reductions in dietary SFA have been found to lower TC and LDL-cholesterol repeatedly [111, 112, 153-155]. As the scores on the SmartDiet questionnaire depends on, among other factors, dietary content of SFA, one would might have expected associations between SmartDiet scores and cholesterol levels. However, no significant correlations were observed, except between TG and SmartDiet scores of the non-FH children.

No significant correlations between SmartDiet scores and lipid levels in the total group of FH subjects were observed. However, the lipid reductions induced in some individuals by the use of statins could have distorted possible correlations between SmartDiet scores and lipid levels. Any correlation observed when investigating the total group of FH subjects would have had to be robust, as 43% of subjects had lipid levels that were affected by drug treatment. However, no significant correlations were observed in either group when those who were statin treated and those who were not were investigated separately. This revealed a general lack of correlations between SmartDiet scores and lipid levels in our study sample. According to the guidelines of Cohen [156], the observed correlation coefficients were small in strength (r = 0.10 to 0.29) or even below, which in the latter case is indicative of no relationship [157].

There may be several reasons for the general lack of correlations. As discussed previously, the fact that the SmartDiet questionnaire and the blood samples were not collected simultaneously may have had significant impact on the results. However, it might also be difficult to detect such correlations at all, if they exist. Tonstad et al found no correlations between lipid levels
of FH children and dietary intakes measured by 4 days dietary record. However, they observed significant correlation between cholesterol intake measured by 24 hour recall and serum cholesterol in boys [152].

The dietary impact on cholesterol levels in FH children might also not be sufficiently large to be caught by the method used in this study. Common to the total group of FH subjects, the group of FH subjects aged 11-15 years and the non-FH children, 50% of SmartDiet score observations were within a range of four points difference, as demonstrated by the 25th and 75th percentiles. As mentioned earlier, at least a 3 points increase is needed to assume an improved diet [124], suggesting the healthiness of diet was quite similar in a large portion of the FH subjects. The narrow range of many of the observations, with relatively few observations belonging in the outer extremes, may have reduced the potential to observe any correlations.

The narrow range may also imply that most young FH subjects perform dietary adjustments to a similar extent, as also supported by the patterns observed regarding choices of food items. However, it may also imply that FH subjects with lower or better scores may have missed out as discussed in another section.

We might would have needed the SmartDiet scores to reflect cholesterol reducing aspects of diet more specifically than what is the case in the questionnaire, in order to observe correlations. The SmartDiet score does not only reflect intakes of dietary SFA, but also of unsaturated fatty acids, sugar and fiber, and the scores of each response option are not given relative to the cholesterol reducing ability of the exact alternative, but in line with healthiness of the single response option relative to the other alternatives in the same food category [124]. Besides, the basis of the SmartDiet score may not include all aspects of diet that should be examined to identify relations between diet and cholesterol levels. As an example, the regular use of a product containing plant sterols, that has shown to reduce cholesterol in FH subjects and normocholesterolemic subjects [115-117], does not contribute to the total SmartDiet score, but is instead investigated by an additional question. Accordingly, it may appear that the SmartDiet score is less suitable to predict the cholesterol reducing effect of diet. Nevertheless, it appears well suitable as a tool for clinical dietary guidance on making food choices aimed at improving healthiness of diet. The simplicity of the questionnaire and the scoring may be a drawback when investigating nutrient content of diet, but an advantage in
clinical settings when time is scarce and a basis for discussing healthy and “heart-friendly” aspects of diet would be beneficial.

The significant negative correlation between TG and SmartDiet scores among the non-FH children may indicate an association between TG and healthiness of diet as measured by the questionnaire. According to the guidelines of Cohen [156, 157], a correlation coefficient of -0.38 is suggested a correlation of medium strength, in line with correlation coefficients from 0.3 to 0.49. The significantly lower SmartDiet scores of the non-FH children compared to the FH children aged 11-15 may suggest that dietary influence on TG has greater impact in lower levels of SmartDiet scores. However, the observation may also be a type-I error, as the risk of observing significant correlations by chance increases in multiple significance testing [158].

5.2.4 Diet and parental FH

Women have been reported to have a healthier diet than men [159, 160] and to be more concerned with healthy eating [161, 162]. In Norkost 1997 it was shown that Norwegian women had significantly higher intakes of vegetables, fruits and skimmed milk than men. O’Doherty and Jensen address a definite correspondence between foods recommended by nutritionists and foods that are perceived as symbolic markers of femininity [160]. They also describe how certain foods apparently function as markers of gender and of gendered status within the nuclear family. In the light of this one might hypothesize that FH children of mothers with FH would have a healthier diet than FH children of a father with FH, as males might appear less concerned with healthiness of diet, while a woman would likely be familiar with and more concerned with having a healthy diet. However, we found no difference in the healthiness of diet measured by the SmartDiet scores, between the FH subjects who had FH from their mother and those who had it from their father. One explanation might be that although the father is the FH-affected parent, the mother may have been involved in dietary consultations in treatment context and might be just as familiar with the dietary recommendations as the affected father is. In a study of marital couples where one had type II diabetes, the affected males were found actively supported by their spouses regarding meal preparations, while the affected females were only passively supported by their husband and more likely to seek out other sources of assistance [163]. Using this as a parallel, a mother would likely facilitate the dietary adjustments recommended to her husband and child.
However, another possibility is that dietary guidance increases the attention to healthy diet in
patients, regardless of gender. Johansson et al found the degree of attention to healthy diet to be strongly and consistently associated with indicators of healthy dietary habits in both sexes [159].

5.2.5 Lipid levels, CRP and parental FH

We found a tendency towards lower apo B/apo A1 ratio, lower TG and higher HDL-C levels in the FH subjects who had paternal FH, suggesting the lipid profile of the group tended to be more favorable than that of subjects who inherited FH through their mother. Resembling results have previously been demonstrated by van der Graaf et al, who found that adult FH subjects with paternal inheritance of FH had a more fortunate lipid profile compared to those with maternal FH [101]. However, the lipid differences observed by van der Graaf et al involved other parameters than those in the present study, namely TC, LDL-C and apo B. The apo B/apo A1 ratio was not mentioned. The observations of Van der Graaf et al were observed in untreated subjects. However, when solely the untreated FH subjects in the present study were analyzed according to parental inheritance, we observed no significant differences in lipid levels or CRP between FH subjects with maternal- and paternal inheritance. This observation is in line with the findings of Tonstad et al who observed no significant difference in either TC, LDL-C, HDL-C, apo B, apo A1 or TG between FH children of dissimilar parental inheritance [100]. Additionally, Napoli et al demonstrated that lipid levels in children of hypercholesterolemic mothers did not differ significantly from those of children from normocholesterolemic mothers [98]. The results are conflicting, possibly due to differences regarding sample sizes or methodology, and the fact that not all studies were conducted on FH children.

However, when we performed similar analyses on FH subjects that were treated with statins we found significantly lower apo B/apo A1 ratio in the FH subjects that had inherited FH from their father. In addition, we observed tendencies towards lower apo B and higher apo A1 and HDL-C, suggesting this group had a more favorable lipid profile than the statin treated FH subjects with maternal inheritance of the disease. The observation could suggest that maternal inheritance of FH predisposes the offspring of gaining higher lipid levels relative to those with paternal FH. A difference between the FH-subjects that were statin treated and those who had untreated lipid values was however the significantly higher age of the treated group. Van der Graaf et al conducted their study on adult subjects, and proposed the increased
age in their study sample relative to that of Tonstad et al was a possible explanation of the different observations. They suggested that what they observed was long term effect of maternally inherited FH [101]. The study sample of Tonstad et al had mean age of 13-14 years [100], in line with the untreated sample in the present study. However, the statin treated FH subjects in our study had significantly higher age which may have given possible long term effects more time to develop. However, such an interpretation should be made with caution, as the study sample of van der Graaf et al had mean ages in the forties, which means they were much older than the statin treated group in our study. In addition, the statin treated subjects in our study had cholesterol values that were manipulated by statins.

There is a possibility that the statin treated groups differ by other means than the different parental origin of the disease. As CVD more often happens at an early age in male FH subjects, and female FH subjects have lower risk of CVD [18], there might be a possibility that more of the FH subjects with paternal FH have a parent with CVD compared to those with maternal FH. As parental CVD is interpreted a sign of increased risk of CVD, there is a possibility that subjects with parental CVD receive more aggressive lipid lowering treatment than those with maternal FH. If more subjects with paternal FH have a parent with CVD, there might be a possibility that more of them also receive more intensive drug treatment, and thus obtain lower lipid levels than those with maternal FH. If this is the case, the higher values observed in those who inherited FH from their mother may reflect less intensive drug treatment rather than a biologic effect of maternal FH.

As CRP is considered a marker of increased CVD risk in adults, and its position as a marker of risk in children is inconclusive, it was of interest to investigate whether FH subjects who inherited FH from their mother, differed in CRP levels compared to those who inherited the disorder from their father. We found no significant differences. One possible explanation is that low grade systemic inflammation level is similar in the two groups of FH subjects. However, CRP has been questioned as a marker of systemic inflammation in FH children [89], meaning that a non-significant difference in CRP may not give much information regarding grade of inflammation in this young group. Studies have demonstrated that CRP levels of FH children are similar to those of non-FH children, but that FH children by other means have a different inflammatory pattern [88, 89]. The results showed that CRP levels of those with maternal and paternal FH were both within reference values, and the values were similar in both groups. However, in our data material CRP was stated as <1 or <0.6 mg/L in
many cases, suggesting the data might not have been sufficiently precise to make small differences detectable. A more sensitive measure of CRP levels could have given more precise results.

Little is known about potential effects of maternal inheritance of FH, as research on the area is limited. However this is a field of further investigation. Eventual differences in CVD risk factors following maternal and paternal inheritance could possibly identify relationships that clinicians should be aware of to optimize individual treatment.
6 Conclusion

In the present study we found that

1) FH children had a healthier diet than non-FH children, when the SmartDiet score was used as measure of healthy diet. Both FH children and the non-FH children had SmartDiet scores that indicated potential to increase healthiness of diet.

2) Among important dietary sources of SFA, FH children tended to choose low-fat products and products that were advantageous to achieve a favorable fatty acid composition of diet in line with a healthy diet. Furthermore, these food choices among FH children differed from those of non-FH children, as the non-FH children to a significantly larger extent chose foods rich in SFA. The use of grain products high in fiber, more than two portions of fruits/berries/vegetables a day and fish for dinner two times a week or more did not differ between the FH children and the non-FH children. The use of sweet spreads/sweet drinks two or more times a day was frequent among FH children, while the non-FH children showed significantly lower use of these items. The majority of both FH children and non-FH children used snacks two or more times a week.

3) The SmartDiet scores of children and young FH subjects and of the non-FH children did not correlate with the lipid levels of the respective groups. The only exception was a medium strength inverse correlation between SmartDiet scores and TG among the non-FH children.

4) SmartDiet scores of children and young FH subjects who inherited the disease from their mother did not differ from the SmartDiet scores of those who inherited the disease from their father. In FH subjects that were not statin treated, lipid levels and CRP of children and young FH subjects who had maternal FH did not differ significantly from the lipid levels and CRP of children and young FH subjects with paternal FH. Among statin treated FH subjects, subjects with paternal FH had significantly lower apo B/apo A1 ratio than FH subjects who inherited the disease from their mother.
Our observations may suggest that the dietary treatment that FH-children receive have beneficial effects on their diet. This may imply that introducing dietary counseling at an early age is of use.

Furthermore, the observed potential of improvement among the FH children regarding healthiness of diet may imply that clinicians could make a greater effort to improve compliance with advices that focus on other aspects of diet besides those concerning fat. The observed higher intake of sweet spreads/sweet drinks among FH children might be something clinicians should notice and take into account in their dietary assessments.

We cannot from this study conclude anything regarding the impact of diet on cholesterol levels in this group of children with generally increased cholesterol levels, but as scientifically based advices regarding what constitutes “heart-friendly” and healthy diet are well established in the literature, recommended dietary treatment should continue.
7 Future perspectives

In this thesis we observed indications that FH children have a healthier diet than other children, but also that the diet of children and young with FH has considerable potential of improvement regarding healthiness. Future investigations should look into potential dietary differences among FH children with the aim of identifying subgroups of FH children that might need more suited dietary treatment in order to achieve a more healthy diet.

Socioeconomic factors such as parental education and parental income have been related to diet. In this study, we were not able to investigate such possible relations due to inadequate sources of data. Future studies should be directed at identifying whether socioeconomic factors contribute to the compliance of a lipid-lowering diet among FH subjects. Likewise, location and population density of residence might be of interest in relation to healthiness of diet in FH patients. Investigation of possible relationships on these areas could possibly identify factors that make it easier or more difficult to have a diet in line with the dietary recommendations. We observed no differences in diet between subjects with maternal and paternal FH, but other family relations could however be related to the diet of FH children, such as having siblings with or without FH and family history of CVD. To which degree the dietary habits of children and young with FH consist when they move out from home could also be an important field of investigation, as moving out suggests less parental influence on diet.

The potential effects of maternal and paternal FH on progression of atherosclerosis and on lipid levels constitute an area of exploration. Future studies should investigate differences in maternal and paternal FH by looking into other inflammatory factors than CRP, as there are indications that other markers of inflammation better reflect inflammation in FH children.

Finally, the lack of documentation regarding the effectiveness of lipid lowering diet on blood lipids in FH patients suggests that large randomized controlled trials should be conducted to investigate the relative effectiveness of lipid lowering diet compared to no dietary intervention. The possible effects of different FH-mutations regarding responsiveness to a lipid-lowering diet is also an unexplored field of investigation that might give insight regarding who could benefit more and less from dietary treatment.
References


46. Unilabs. *serum - Lp(a), Lipoprotein (a) [cited 2012; Available from: http://www.unilabs.no/For-fagpersonell/Anvisningar123/Klinisk-Kemi/L/Lpa/?print=true.*


Appendices

Appendix 1. Approval from the Regional Committee of Medical Ethics

Regional komité for medisinsk og helsetaglig forskningsetikk Sør-Ost A (REK Sør-Ost A)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 84 46 66
Telefaks: 22 84 05 90
E-post: jorgen.karlsen@medicin.uio.no
Nettadresse: http://helseforskning.etikkom.no

Seksjonsoverlege dr. med Leiv Ose
Lipidklinikken
Rikshospitalet

Dato: 23.8.2010
Deres ref.: 
Vår ref.: 2009/1343a

2009/1343a Tidlig inflammasjonsmarkører hos barn med familiær hyperkolesterolemie.

Prosjektleder: Seksjonsoverlege Leiv Ose, Lipidklinikken, Rikshospitalet

Forskningsansvarlig: OUS, Rikshospitalet

Vi viser til brev datert 01.07.2010 vedlagt revidert informasjonskriv med samtykkeerklæring, samt til ettersendt spørreskjema mottatt 9.8.2010

Endringen innebærer at kostregistreringsskjemaet “Smart Diet” skal fylles ut.

Vedtak:

Komiteen har ingen merknader til revidert informasjonskriv og tar til orientering at vilkår for godkjennelse er oppfylt.

Komiteen godkjenner at prosjektet videreføres med den endringen som er beskrevet og i samsvar med de bestemmelsene som følger av hels forskningsloven med forskrifter.

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

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personverna og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Personidentifiserbare data slettes straks det ikke lenger er behov for dem og senest ved prosjektets avslutning.

Prosjektet skal sende sluttmelding på eget skjema, se hels forskningsloven §12, senest et halvt år etter prosjektstilt.

Vi ber om at alle henvendelser sendes inn via vår saksportal http://helseforskning.etikkom.no eller på e-post til post@helseforskning.etikkom.no

Vennligst oppgi vårt saksnummer/referansenummer i korrespondansen.

Med vennlig hilsen

Gunnar Nicolaysen (sign)
Professor
Leder

Anne Schiotz Kavli
Forståekonsulent

Kopi: Oslo universitetssykehus: godkjennings@rikshospitalet.no
Appendix 2. Information letter that was sent to the invited FH subjects

Rikshospitalet - Radiumhospitalet HF

Medisinsk klinikk
Avd. for forebyggende med.
Lipidklinikk, RH

Sendt til:

Postadresse
0444 Oslo

Besøksadresse:
Sognsvannsv. 20
Sentralsjøen: 02770

Vår ref.:
Skrevet dato:

RRHF
Org.nr. NO 987 399 708 MVA

INFORMASJON OM FORSKNINGSPROJEKT

Vedlagt følger informasjon om et forskningsprosjekt. Vi ønsker å studere informasjon som er i sykehusjournalen din på Lipidklinikkken, men kun dersom du tillater det. Slik tillatelse må gis skriftlig og må returneres til oss i vedlagte frankerte svarkonvolut.

Vi tror dette forskningsprosjektet vil gjøre det mulig å forstå mer om faktorer som resulterer i avleiringer i blokkåret (åreforkulking).


Dersom du gir din tillatelse gjelder den kun for dette ene forskningsprosjektet. Skulle det være behov for slikt innsyn i en ny studie, må vi be om nytt samtykke for det.

Prosjektet er mer detaljert beskrevet i "Informert samtykke" som er vedlagt. Hvis du blir med på dette forskningsprosjektet ber vi deg returnere ett underskrevet og datert eksemplar av det informerte samtykke og det ferdigutfylte Smart Diet skjemaet. Det andre eksemplaret av det informerte samtykke beholder du.

Vi håper at det er i orden at vi tar kontakt på telefon dersom vi ikke hører fra deg.

Vennlig hilsen

Leiv Ose
Seksjonsoverlege dr. med.
(sign)

Dokumentet er produsert og signert i elektronisk pasientjournal

76
Appendix 3. Informed consent scheme that was sent to FH subjects

**Appendix 3. Informed consent scheme that was sent to FH subjects**

**Forespørsel om å delta i forskningsprosjektet ”tidlige inflammasjonsmarkører hos barn med høyt kolesterol”**

Dette er en forespørsel om å delta i et forskningsprosjekt hvor vi ser på betydningen av fettstoffer i blodet for andre risikomarkører som f.eks betennelsesstoffer hos barna med arvelig høyt kolesterol.

Før dere bestemmer dere før om dere vil delta, er det viktig at dere forstår hvorfor studien gjennomføres, hva den innebærer og hvilke fordeler, risikoer og uebahg som kan være forbundet med den. Dere bør lese denne informasjonen nøye og spør gjerne en av de prosjektansvarlige om ting du er usikker på.

**Bakgrunn**

Forhøyet kolesterol er en risikofaktor for hjerte-kar sykdom, fordi kolesterol avleires i pulsåreveggen. Det tar flere årter å “bygge opp” kolesterolavleiring slik at det blir sykdom. Barn som er født med forhøyet kolesterol er spesielt utsatt for kolesterolavleiring. Vi vet lite om når kolesterolavleiringen starter, men vi tror at vi kan påvirke denne prosessen tidlig f. eks hos barn og ungdom med familieht forhøyet kolesterol.

Ny forskning har vist at hjerte-karsykdom er en betennelsesprosess. Betennelse kan utløses av høyt kolesterol i seg selv, men også andre faktorer kan bidra. Å redusere betennelsesprosessen kan være en ny måte å redusere kolesterolavleiringer i blodåreveggen på. Man kan tenke seg at dette kan redusere risikoen for hjerte-kar sykdom.

Du har tidligere vært til undersøkelse på Lipidklinikken fordi du har arvelig høyt kolesterol (FH). Grunnen til at vi kontakter deg nå er at vi vil undersøke om nivået av betennelsesstoffere i blodet er relatert til kolesterol nivået og type arvelig form for høy kolesterol. Vi ønsker å bruke allerede eksisterende kliniske opplysninger i journalen for å studere sammenhenger mellom kolesterol nivå, nivå av betennelsesmarkører, type arvelig form av kolesterol, familiehistorie osv

**Du trenger derfor ikke å møte opp på Lipidklinikken eller foreta deg noe for å være med i denne studien**

**Hvem vi søker**

- Barn (6-18 år) med arvelig høyt kolesterol som har vært i konsultasjon på Lipidklinikken i årene 2000-2010 og i den forbindelse avlagt en blodproøve.

**Hva vil dette bety for barnet ditt?**

- Barnet trenger IKKE møte opp på Lipidklinikken.

**Deltagelse er frivillig**

- Det er frivillig å være med i studien. Du kan når som helst trekke barnet ditt uten å oppgi grunn. Deltakelse medfører ingen ubehag for barnet siden vi ønsker å bruke allerede
eksisterende kliniske opplysninger i journalen og disse opplysninger allerede er tilgjengelig på Lipidklinikken.

Hva skjer med informasjonen som samles inn om barnet ditt?
Vi ønsker å bruke allerede eksisterende kliniske opplysninger i journalen for å studere sammenhenger mellom kolesterol nivå, nivå av betennelseresmarkører, type arvelig form av kolesterol, familiehistorie osv. Forskerne er underlagt tusshetsplikt, og alle opplysninger som nedtegnes blir behandlet strenget konfidensielt. Alle forskningsdata vil være aidentifiserte. Aidentifisert betyr at ingen utenforstående får vite hvem som har deltatt i studien men gir ansvarshavende for prosjektet (se under) mulighet til å koble sammen journaldataene fra den enkelte forsøksprosoperson som dataene er hentet fra. Opplysninger som fremkommer i sluttrapporten og i artikler vil ikke kunne tilbakeføres til enkeltpersoner.

Dersom du ønsker å delta her vil du sende tilbake underskrevet samtykke i vedlagte frankerte svar konvolutt. Dersom du ikke ønsker å delta trenger du ikke foreta deg noe.

Dersom du ønsker ytterligere informasjon er det bare å ta kontakt med en av de undertegnede

Seksjonsoverlege dr med. Leiv Ose, Lipidklinikken, Oslo Universitetssykehus,
Tel: 23 07 56 14
Professor dr philos. Kirsten Bjørklund Holven, Avd for Ernæringsvitenskap, Universitetet i
Oslo, tel: 22 85 13 61

Andre viktige opplysninger
- Prosjektet finansieres av driftsmidler fra Universitetet i Oslo. Det vil bli sett støtte til
prosjektet fra ulike forskningsfond. De prosjektansvarlige har ingen økonomiske
interesser i prosjektet.
- Etter gjeldende regler er studien blitt vurdert av Regional komité for medisinsk
forskningsetikk,
- Ved eventuelle spørsmaal for, under eller etter studien kan du kontakte en av de
prosjektansvarlige (se nedenfor).
- Ansvarshavende for prosjektet er Seksjonsoverlege dr med. Leiv Ose, Lipidklinikken,
Oslo Universitetssykehus (e-post: leiv.ose@rikshospitalet.no; Tel: 23 07 56 14) og
Professor Kirsten B Holven, Avdeling for ernæringsvitenskap, Institutt for medisinske
basalfag, Universitetet i Oslo (e-post: kirsten.holven@medisin.uio.no, tel 22851361).

Ytterligere informasjon om studien finnes i kapittel A – utdypende forklaring av hva
studien innebærer.
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B –
Personvern, biobank, økonomi og forsikring.

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

Inklusjon/eksklusjonskriterier:
Følgende forhold må være oppfylt for å delta i studien:
Inklusjonskriterier:
- Barn med arvelig høyt kolesterol som har vært i konsultasjon på Lipidklinikken i perioden mellom 2000-2010.

Kapittel B - Personvern, biobank, økonomi og forsikring

**Personvern**

**Biobank**
Det vil ikkje bli opprettet biobank siden vi kun skal bruke allerede eksisterende opplysninger som finnes i journalen.

**Utlevering av materiale og opplysninger til andre**
Hvis du sier ja til å delta i studien, gir du ditt samtykke til at informasjonen fra journalene kan benyttes av de prosjektansvarlige samt andre samarbeidspartnerne i prosjektet.

**Rett til innsyn og sletting av opplysninger om deg og sletting av prøver**
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om barnet ditt. Du har videre rett til å få korrigeret eventuelle feil i de opplysningsene vi har registrert. Dersom du trekker barnet ditt fra studien, kan du kreve å få slettet innsamlede opplysninger.

**Økonomi**

**Forsikring**
- Det er ikkje behov for særskilt forsikring i denne studien.

**Informasjon om utfallet av studien**
Resultatene fra studien vil bli publisert i fagtidsskrifter og presentert på nasjonale og internasjonale fagmøter.
• Ansvarshavende for prosjektet er Seksjonsoverlege dr med. Leiv Ose, Lipidklinikken, Oslo Universitetssykehus (e-post: leiv.ose@rikshospitalet.no; Tel: 23 07 56 14) og professor Kirsten B Holven (e-post: kirsten.holven@medisin.uio.no, tel 22851361),

Samtykke til deltakelse i studien

Jeg godkjenner at mitt barn deltar i studien

(Signert av en av barnets foreldre, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert av prosjektansvarlig, dato)
Appendix 4. The SmartDiet questionnaire
De gode rådene finner du her

Mettet fett er kolesterolendende. Reduser derfor innantaket av matvarer med mye mettet fett. Velg i stedet matvarer med umettet fett som kan senke kolesterolølet.

Drikke mager melk, ½ liter skummet, øl eller sur, daglig. Dersom du ikke drinker melk daglig, kan det føre til et lavt innhold av kalsium.

Alle frite- og rommelretter inneholder mye mettet fett og antakelig ikke i henderskostholdet. Cultura, skummet kultur, lettmat, ekstra lett melk, skummet melk, yoghurt, mager Créme Fraiche (10 % fett) og Kesan (1 % fett) kan brukes i matlaging, til sauser og dressing.

Ost er en kilde til store mengder mettet fett. Velg lettere eller mager ost (ost med mindre enn 10 % fett) til hverdags. Ikke bruk lettere ost som pålegg på mer enn en tredel av dagens broder/skiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen. Velg gjerne plantebaserte ostet som pålegg og i matlagingen.


Spis alle typer fisk til middag flere ganger i uken. Fisk som makrel, sild, laks og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig. Spis fisk som pålegg daglig. Ta i regelen 1 skje tran, eventuelt 2 fiskelegjerapører, daglig året rundt.

Bruk grønne majones pålegdag daglig, men i moderate mengder. De fleste majonesprodukter inneholder mye olje og derfor mye fett (og kalorier), men fettet er umettet og derfor gunstig.

Myk plantamargarin er en god kilde til umettet fett. Velg typer med mer enn 70 % umettet fett. Velg grønne margarin med plantesteroler. Plantesteroler er gunstig for kolesterolølet. Ved bruk av medikamentet Ezetrol® (ezetimib) forventes imidlertid ikke plantesteroler å gi noen ytterligere kolesterolreduksjon.

Bruk gjerne olje, flytende eller myk plantamargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg hellet kott eller ovnstekt mat, da vil behevet for fett i matlagingen reduseres.

Grove komprodukter er viktig i henderskostholdet. Spis mye av alle sorter fibrike komprodukter. Havre er spesielt gunstig og bor brukes regelmessig. Brodet bor inneholde mer enn 6 gram fiber pr. 100 gram brød. Se også etter Bredskalså i emballasjen.


En porsjon poteter, ris eller pasta daglig er et fint tilbehør til middagen.

Bruk minst mulig sukker, sukkerholdig mat og drikke, som lekes, kaker, is, sett pålegg, sukker-godt, sjokolade, juice, nektar, saft og brus. Med unntak av fruktjuice gir disse produktene ingen eller få næringsstoffer, men kan bidra til økt vekt. Sukker (inkludert fruktssukker) kan også øke triglycerideriene.


Kaffebønnen inneholder fettstoff som elver kolesterolølet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert, da filteret fjerner det meste av fettsstoffene. Husk at kaffe tasakt fett (for eksempel café latte, cappuccino) kan være en kilde til mettet fett avhengig av melktypen som brukes og mengde kaffe som drukkes.

Alkohol inneholder mye kalorier og kan derfor føre til veke, alkohol kan også øke triglycerideriene.

Eggeplommer inneholder mye kolesterol. Begynner innantaket til to eggeplommer per uke. Den største årsaken til økning av kolesterolølet i blodet er likevel matvarer rike på mettet fett.

Spørseskjaften vil ikke nødvendigvis gi et komplette bild av dette kostholdet. Du kan få mer informasjon om kostholdet i fæt.: Kostbehandling ved høye blodlipider hos voksne (Lipidkliniken 2008).

Spørsmål 1-15 med unntak av spørsmål 10 er evaluert i forhold til ved kosterholdregistrering.


26 spørsmål om dit kosthold og din livsstil

Copyright: Ljudkliniken, Medinnova, Rikshospitalet, Oslo Universitetssykehus. Kapering av dette skjermalet er ikke tillatt.

Les spørsmålene og de angitte svaremulighetene nøye!

Sett kryss ved det svaret som passer best med det du vanligvis spiser.

Kommentarer: 

Antall poeng:

Kostholdsvurdering

27 poeng eller mindre: Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig.

28-35 poeng: Du kan forbedre kostholdet ditt på ett eller to punkter, slik at det blir mer helse- og hjertevennlig.

36 poeng eller mer: Du har en initially kostholdsmå.

SmartDiet™
7. Fisk til middag
Hvor mange ganger i uken spiser du fisk, fiskemait og/eller fiskemæl? Antall:
Innt i en gang i uken eller aldri 3 eller flere ganger i uken 2 ganger i uken

8. Mejseme, remodulering og kwatær
Hvordan bruker du mejselproteiner, remodulering eller kwatær på brødplanet?
Eksempler: Mejesmør, kwatær eller lavemæl 2-3 ganger i uken

9. Sjømat eller margarin på brødplanet
Hvilken type bruker du?
Eksempler: Margarin, margarin eller margarin

10. Planterester
Bruger du et produkt som inneholder planterester?
Eksempler: Vita Pro-aktiv eller Baal Pro-aktiv

11. Fett i matlagingen
Hvilken type fett bruker du?
Eksempler: Full fleks, flaks, olivenolje

12. Brød, knekkebrød og andre komponenter
Hvor mange skår brød, rustikkbrød, knekkebrød og/eller spiser du daglig?
Eksempler: Rustikkbrød, knekkebrød eller spiser du daglig

13. Grønnsaker, frukt og bær
Hva er det mest populære grønnsak, frukt og/eller bær du spiser daglig?
Eksempler: Løk, grønnsak eller frukt

14. Søtt pålegg og søt dricka
Hvordan bruker du sot pålegg eller søt drinker?
Eksempler: Sot pålegg eller søt drinker

15. Fiskepålegg
Hvor ofte har du fisk som pålegg eller i salater til lunch?
Eksempler: Laks, makreler, sjokolade eller fiskepålegg

16. Bälgkastor
Spisar du bälğıskastor utkostat?
Eksempler: Hals, tonsaker eller våtmat

17. Potet, ris og pasta
Hvor mange ganger spiser du potet, ris og pasta?
Eksempler: Potet, ris og pasta

18. Nettet, mandler og øl
Spiser du netter, mandler eller øl?
Eksempler: Nettet, mandler eller øl

19. Kaffe, te og liknende
Hva spiser du i kaffestu?
Eksempler: Kaffe, te eller liknende

20. Alkohol
Drinker du alkohol?
Eksempler: Kaffe, te eller liknende

21. Egg
Hvor mange egg spiser du i uken?
Eksempler: Laks, makreler, sjokolade eller fiskepålegg

1. Meik (eur) og yoghurt
Hvor mange ganger spiser du meik og yoghurt i dag?
Eksempler: Meik eller yoghurt

2. Fjøse, røke, kjøtt, ost
Hvilken type fjøse, røke, kjøtt, ost bruker du?
Eksempler: Fersk fjøse, eller røke

3. Ose på breddet, matlagingen, på pizza o.l.
Hva er det mest populære påse eller i salater?
Eksempler: Laks, makreler, sjokolade eller fiskepålegg

4. Kjøttplagg
Hvordan bruker du kjøttplagg?
Eksempler: Kjøttplagg eller salater

5. Kjøtt til middag
Hvilken type kjøtt bruker du?
Eksempler: Kjøtt eller salater

6. Flisepålegg
Hvor ofte har du fisk som pålegg eller i salater til lunch?
Eksempler: Laks, makreler, sjokolade eller fiskepålegg
**Appendix 5.** A short form to identify medication, presence of chronic disease, history of hospitalization and possible presence of cardiovascular disease in the family, sent to invited FH subjects

---

**Dato for utfylling av skjema:** ____________

Skjemaet bes levert utfyltt ved

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<th>Ditt navn:</th>
<th>Fødselsnr:</th>
<th>Boligadress</th>
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1. **Har du vært innlagt på sykehus noen gang?**

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<td></td>
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<td>Sykehus</td>
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2. **Bruker du medisiner**

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<th>Navn på medisinen</th>
<th>Start (år/mnd)</th>
<th>Tablettsyrke</th>
<th>Antall per dag</th>
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3. **Har du noen kronisk (langvarig) sykdom eller plage?**

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4. **Har du fått kostveiledning tidligere?**

<table>
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<th>JA</th>
<th>NEI</th>
<th>Hvis ja når, og av hvem? ___________________</th>
</tr>
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</table>

**BESKRIV KORT ARVELIGE FORHOLD**

1. **Har noen i din familie hatt en brå død for 70 år som muligens kan skyldes hjerteinfarkt eller slag?**
Forespørsel om å delta i forskningsprosjektet ”betennelses-stoffer i blodet og hvite blodceller ved høyt kolesterol”

Lipidklinikken ønsker å undersøke hvite blodlegemers evne til å produsere forskjellige betennelses stoffer hos barn og ungdom med familær hyperkolesterolem (FH), som ikke er behandlet med kolesterolenkende medisin. Vi vil undersøke om blodcellene produserer forskjellige betennelses stoffer hos FH barn sammenlignet med friske barn, og om dette er relatert til kolesterol nivået. Hjerte-karsykdom er en av de hyppigste årsakene til sykdom hos voksne i dag.


Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og aidentifiserte opplysninger utleveres til de forskningsinstitusjonene som er samarbeidspartnerne i prosjektet.

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.

Det er opprettet en biobank der den aidentifiserte blodprøven vil inngå. Wenche Reed er biobankkoordinator ved Forskningsstøtteavdelingen RR-HF med ansvaret for biobanken. Einar Hysing er databehandlingsansvarlig etter personopplysningsloven/helseregisterloven. Kontaktperson for prosjektet er forsker Kirsten Holven ved Aveling for Ernæringsvitenskap, Institutt for Medisinske Basalfag, Universitetet i Oslo, telefon 22 85 13 61 eller e-mail: kirsten.holven@medisin.uio.no.
Jeg/Vi har lest og forstått informasjonsskrivet vedr.prosjektet "betennelses-stoffer i blodet og hvite blodceller ved høyt kolesterol" og er villig til å delta.

Barnets fødselsnummer til blodprøvetaking:

Deltagers foresatte må samtykke der barnet er under 16 år

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