Long term follow-up of patients with Familial Hypercholesterolemia after participation in clinical trials in childhood: an exploratory study

Adherence to treatment and dietary advices

Master Thesis

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Department of Nutrition, Faculty of Medicine

UNIVERSITY OF OSLO

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Ida Halvorsen

Summary

Background and aims: Familial hypercholesterolemia (FH) is an inherited, metabolic, autosomal dominant disorder. It is characterized by abnormal high total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The elevated LDL-C levels are caused by mutations in genes affecting the LDL receptor. The risks of atherosclerosis and premature cardiovascular disease in patients with FH are extremely high due to the poor lipid profile. To date, there is limited experience and knowledge about treatment of FH in children, and which requires further investigation. This thesis aims to identify effects of monitoring of participants involved in previous trials at the Lipid Clinic when they were children. Objective and subjective parameters were both evaluated in order to detect factors of importance regarding the development and handling of the disease.

Subjects and methods: This was a systematic clinical exploratory follow-up study, which included both retrospective and present measurements. 67 adults (>18 years), who had previous participated in clinical trials when they were children, were recruited. LDL-C levels were compared in several different groups and subgroups, among other between (1) statin users versus non-statin users, (2) gender, (3) according to outpatient control routines, (4) medication routines and (5) SmartDiet score. We also investigated subjective parameters, among other reasons for poor adherence and not taking cholesterol-lowering medication.

Results: 19 out of 67 participants (28%) did not use statins at time of follow-up. Statin users had a significant lower LDL-C level than non-statin users ($P < 0.001$). The reduction in LDL-C level among statin users from time of diagnosis to follow-up were 50%, but only 12.8% of the statin users achieved the treatment goal of LDL-C $\leq$2.5 mmol/L. Both genders had a significant reduction in LDL-C and TC levels ($P < 0.001$). Females had a greater reduction in LDL-C levels than males (55% and 23%, respectively). No explanations for the greater reduction in females were found. There was also a significantly lower LDL-C level in participants who had their last outpatient control during the last two years before our follow-up ($P = 0.044$), and a numerical lower LDL-C level in those who had an outpatient control every two years or more often compared to participants with less frequent outpatient controls ($P = 0.069$).

Conclusion: The great difference in lipid parameters between statin users and non-statin users illustrates the importance of adequate and continuous medical treatment when diagnosed with FH. Further research may be beneficial to explore why females had greater reduction in LDL-C level than males in our follow-up. FH is a chronic disease, and this present study shows the importance of good outpatient control routines in children (<18 years) and young adults.

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Abbrevations

ApoA-1	Apolipoprotein A-1
ApoB-100	Apolipoprotein B-100
ApoB/ApoA1 ratio	Apolipoprotein B-100/ApolipoproteinA-1 ratio
ASAT	Aspartate amino transferase
ALAT	Alanine transaminase
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CVD	Cardiovascular disease
FDB	Familial Defective Apolipoprotein B-100
FH	Familial hypercholesterolemia
HeFH	Heterozygous Familial hypercholesterolemia
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HMG CoA	3-hydroxy-3methyl-glutaryl Co-enzyme A
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein (a)
MI	Myocardial infarction
OUS	Oslo University Hospital (Oslo Universitetssykehus)
REK	Regional Etical Comitee
SD	Standard deviation
TC	Total cholesterol

TG	Triglycerides
VLDL	Very low-density lipoprotein

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1. Introduction

1.1 Cholesterol

The main functions of cholesterol in the human body is as a component in the structure and function of all human cells, and as a precursor of bile acids, steroid hormones and Vitamin D (1). It is therefore of critical importance that all the cells in the human body achieve a sufficient supply of cholesterol. A complex series of transport, biosynthetic, and regulatory mechanisms has been evolved to meet this need (2-4).

Cholesterol is insoluble in the blood and it is therefore carried in distinct particles, called lipoproteins.

1.2 Lipoproteins

Lipoprotein particles contain both lipid and proteins. They have a hydrophobic core of triacylglycerol and cholesterol ester and a hydrophilic outer surface of phospholipid and free cholesterol. The lipoprotein packs the hydrophobic cholesterol in the center of the particle, while the hydrophilic outer surface makes it soluble and transportable in the bloodstream, thus cholesterol can be transported to and from the tissues (2, 3). There are primarily two different classes of lipoproteins in the cholesterol metabolism: (1) those containing apolipoprotein B-100 (ApoB-100) such as very low-density protein (VLDL), VLDL remnants, intermediate-density lipoproteins (IDL) and low-density lipoproteins (LDL), and (2) those containing apolipoprotein A-1 (ApoA-1) such as high-density lipoproteins (HDL). In addition, chylomicrons contain ApoB-48. In human blood LDL cholesterol (LDL-C) usually dominates with up to 60-70% of the total serum cholesterol (TC), while HDL cholesterol (HDL-C) makes up 20-30% (2). TC, HDL-C and LDL-C are commonly measured in clinical practice.

LDL

LDL is a particle with low density, and transports cholesterol to peripheral tissues in the body. The LDL particle has a high concentration of cholesterol and cholesterol esters (2). LDL-C is often called “bad cholesterol” because of its strongly atherogenic effect (3). To reduce the atherogenic development in blood vessels, LDL-C is the major target of cholesterol-lowering therapy.

HDL

HDL is a particle with high density, and transports cholesterol from peripheral tissues to the liver. HDL-C is often called "good cholesterol". Low levels of HDL-C correlates with an increased risk of atherosclerosis and coronary heart disease (CHD) events, while high levels of HDL-C have shown protective effects (3).

Lipoprotein (a)

Lipoprotein (a) (Lp(a)) is an altered form of LDL that contains the ApoB-100 portion of LDL linked to ApoA-1. Lp(a) and a LDL particle are nearly identical in structure. Increased levels of Lp(a) are associated with higher risk of coronary and cerebrovascular disease, independent of TC and LDL-C levels (1). The mechanism whereby Lp(a) may be particularly atherogenic is through its binding and transportation of phospholipids (5).

1.3 Apolipoproteins

Apolipoproteins are proteins that bind lipids to form lipoprotein, and thereby transports lipids in serum (6).

The LDL particle includes a single apolipoprotein, called ApoB-100. ApoB-100 is the major apolipoprotein of all atherogenic lipoproteins, such as LDL, VLDL and intermediate-density lipoproteins (IDL). High levels of total serum ApoB-100 is associated with coronary atherosclerosis and CHD events, and is proposed as an alternative to elevated levels of LDL-C as risk factor (3, 6).

ApoA-1 is the major protein component of HDL-C and it is an important contributor to the removal of cholesterol and fats from the blood, and thereby preventing atheroma. It is usually low when HDL is reduced, and a low ApoA-1 is associated with increased risk for CHD, but not independently of low HDL (1, 3, 4, 6).

ApoB-100 and ApoA-1 have opposite effects on atherogenic risk, and the ratio between the two values, ApoB-100/ApoA-1, is often measured as a predictor of the risk for CHD (6). Two studies, the Swedish AMORIS study and the large case-control INTERHEART study, reported that ApoB-100/ApoA-I ratio is a significantly better indicator of CHD than any of the conventional cholesterol values (7, 8).

1.4 Cholesterol- and lipoprotein metabolism

The human body obtains the cholesterol both exogenously and endogenously. Dietary cholesterol is absorbed in the gut, primarily in duodenum and jejunum. When it passes the enterocytes, the cholesterol is transported in the bloodstream to the liver packed in chylomicrons. The chylomicrons are rich in triglycerides, have a hydrophilic outer surface and are therefore able to be transported in the bloodstream. The body itself also synthesizes cholesterol, mainly in the liver, but also from gut and the central nervous system, by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the rate limiting step in the cholesterol biosynthesis and catalyzes the precursor to cholesterol. From the liver, cholesterol and triglycerides (TG) are secreted into the bloodstream as VLDL and converted to LDL in the circulation by lipoprotein lipase. LDL further transports the cholesterol to peripheral tissues in the body. The uptake of cholesterol in the human cells is mediated by LDL receptors (LDLR) (2, 9).

The LDLR is a transmembrane protein and is present in almost all tissues. It controls the cholesterol homeostasis by several complex mechanisms. These processes include synthesis of the receptor in endoplasmic reticulum, migration of the receptor protein to the cell surface, binding of the LDLR to plasma LDL via ApoB-100 etc. (6).

HDL removes excess cholesterol from tissues and facilitates the transport to the liver for degradation and/or excretion. This process is called reverse cholesterol transport. Cholesterol is further absorbed into the liver in two different ways: (1) either directly uptake from HDL via the hepatic class B scavenger receptors, or (2) via hepatic LDLR where the HDL particles in advance are transformed into LDL and VLDL. Cholesterol is excreted in the bile, both as free cholesterol and as bile acids (2, 3, 9).

High blood cholesterol levels and/or various defects in the cholesterol metabolism may lead to lipid accumulation and atherosclerosis.

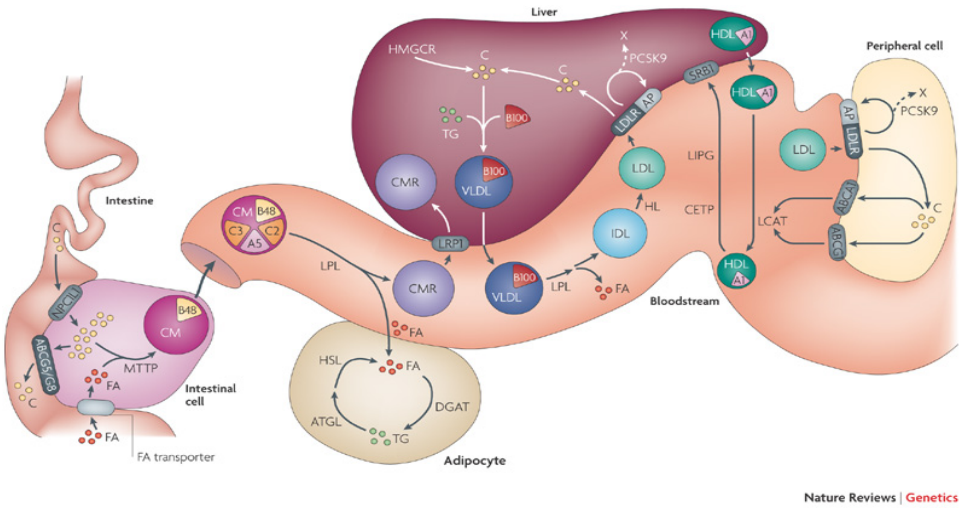

Figure 1. Lipoprotein metabolism. Adapted from Nature review genetics (10).

1.5 Atherosclerosis

Intimal thickening and lipid accumulation are the key processes in atherosclerosis (11). Circulation of LDL particles may initiate the atherosclerotic process by penetrating into the arterial wall. When LDL is passing the sub endothelial space of the arterial wall, it is modified in many different ways (6). Modified LDL in the arterial wall recruits phagocytic white blood cells, monocytes, which stimulates an inflammatory response and results in accumulation of plaque. Atherosclerotic plaques have three principal components: (1) cells, (2) extra cellular matrix (ECM) and (3) intracellular and extracellular lipids. The major cells involved in the atherosclerotic process are smooth muscle cells, macrophages and T cells. The ECM includes collagen, elastic fibers and proteoglycans (12).

When the monocytes reach the tissue they are differentiated to macrophages which ingest oxidized cholesterol and become foam cells and fatty streaks. The fatty streaks are the first grossly visible atherosclerotic lesions (6, 12). They are further developed and converted into fibrous atherosclerotic plaques, followed by smooth muscle formatting and collagen deposition, illustrated in **figure 2** (6).

Accumulation of plaque leads to narrowing and loss of elasticity in the blood vessel wall, and are very susceptible to rupture which can lead to acute coronary syndrome (6).

In addition to elevated circulating LDL-C (>4.2 mmol/L) and decreased HDL-C (<1.0 mmol/L) there are many other risk factors for atherosclerosis, including cigarette smoking, elevated systolic blood pressure (BP) (>140 mm Hg) and diabetes (6).

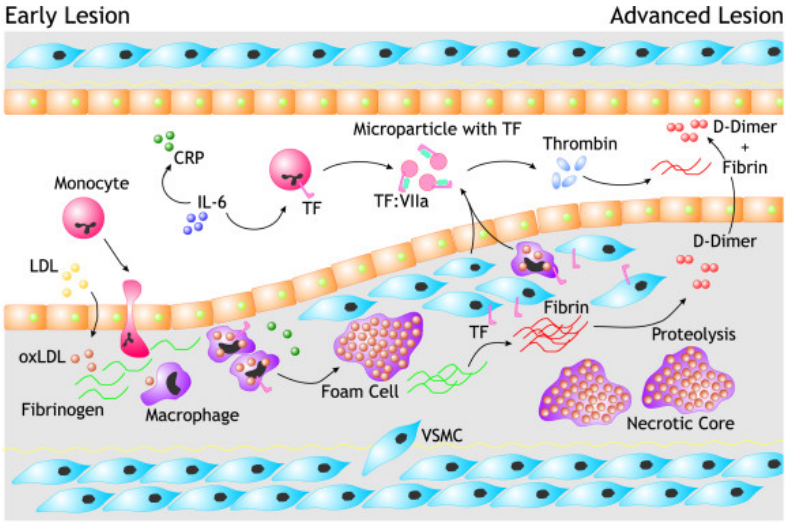

Figure 2. Inflammation and atherosclerosis**.** Adapted from Stronk et al (13).

1.6 Ischemic Heart Disease

Ischemic heart disease (IHD) is a generic term for a group of syndromes resulting from myocardial ischemia. Ischemia occurs primarily due to reduction in coronary blood flow caused by obstructive atherosclerotic disease. IHD is also frequently called coronary artery disease (CAD). CAD is one of the leading causes of death and disability worldwide (11, 14, 15). In 2011 the most frequent of death causes was IHD, reflecting 11.2% of all deaths (15).

The basic clinical syndromes of IHD are categorized in four groups, angina pectoris (stable or unstable), acute myocardial infarction (MI), chronic IHD (progressive heart failure) and sudden cardiac death (SCD). Unstable angina, acute MI and SCD are the three catastrophic manifestations of IHD, and have the generic term acute coronary syndrome (11).

IHD is often caused by a combination of preexisting atherosclerotic obstruction of coronary arteries and new superimposed thrombosis and/or vasospasm. The initiating event to acute coronary syndrome is typically disruption of a plaque due to rupture, fissuring or ulceration of plaques and/or hemorrhage into the core of plaques (6, 11).

1.7 Familial Hypercholesterolemia

1.7.1 Definition FH

Familial hypercholesterolemia (FH) is an inherited, metabolic, autosomal dominant disorder characterized by abnormally high LDL-C levels (16, 17). The condition can either be heterozygous familial hypercholesterolemia (HeFH) which is caused by inheritance of a defective gene from one parent, or homozygous familial hypercholesterolemia (HoFH) which is caused by inheritance of a defective gene from both parents (18).

Subjects with HoFH have an extremely high risk for atherosclerosis and if untreated most individuals will experience IHD in childhood or adolescence. HoFH is a much more severe clinical disorder than HeFH (15, 19).

Elevated LDL-C levels in HeFH is caused by defects in at least one of the many different genes that code for proteins that affects the normal control of lipoprotein metabolism (20). The most common (85-90%) is heterozygous loss of function mutations in LDLR gene, located on chromosome 19p13.1-13.3. Other heterozygous mutations are (1) mutations in the ApoB-100 gene which impair the LDLR binding domain of ApoB-100 (located on chromosome 2p23-24), and (2) gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) which gives a new abnormal function (located on chromosome 1p32) (17).

1200 different mutations in LDLR have been described, affecting different steps in the LDLR biogenesis (21). It results in a dysfunctional LDLR on the cell surface of the hepatocytes. The LDLR on the hepatocytes are required for uptake of LDL particles from the circulation to the liver, and thus inactivation and degradation of cholesterol in the body (17). A dysfunctional LDLR will make the liver unable to absorb sufficient amounts of LDL-C from the bloodstream, and LDL-C levels will be elevated (21).

Defects in genes of ApoB-100 and PCSK9 represent about 5-10% of the FH cases (17). Mutations in the ApoB-100 gene region, that encodes the LDLR binding domain, reduce the binding affinity for the LDL particles to the LDLR and the removal of LDL-C from the circulation (22). FH caused by a mutation in the ApoB-100 gene region is apparently less severe than FH caused by mutations in LDLR gene (17). PCSK9 is a serine protease that

regulates the degradation of the LDLR, and consequently plays an important role in regulating the cholesterol into the cells. Circulating PCSK9 binds the LDLR on the cell surface and then incorporates with the LDLR. Mutations in PCSK9 lead to a gain-of-function phenomenon, and a higher rate of LDLR degradation (23). Mutations in PCSK9 is the least common of the three mentioned (17). Individuals with loss-of-function mutations in PCSK9 have reduced plasma levels of LDL-C and are therefore protected from CHD. These findings have validated PCSK9 as a therapeutic target and suggested new approaches for the treatment and prevention of CHD (23).

The life-threatening effects of both HeFH and HoFH are related to the resulting elevation in plasma LDL-C, with consequent cholesterol retention in the arterial wall and foam cell formation within the intima of arteries. This may further lead to an occlusive atherosclerosis (21).

1.7.2 Prevalence

HeFH is quite common with a prevalence of 1 per 300-500 in many Western countries, while HoFH is a less frequent disease with an estimated prevalence of 1 per 1 million (17, 21). To estimate the incidence of FH is hard, partly because FH is not attributed an independent code in the World Health Organization International Classification of Diseases and partly because FH is an underdiagnosed disease (21).

Although FH occurs in all populations, some ethnic groups are disproportionately impacted, where there are founder effects and relatively isolated populations. These include people of Lebanese, French Canadian, South African and Ashkenazi Jewish descent. In these populations FH may be found as frequently as 1 in every 80-100 people (24, 25).

Earlier studies have found 1:1 relationship in definite and probable FH in men and women of age below 60, while there is a higher prevalence of FH in women at age 60 plus. This suggests that a higher number of men FH suffer death of premature cardiovascular diseases (CVD) than women (21).

1.7.3 Criteria of FH

Table 1. The Dutch Lipid Clinic Network criteria for diagnosis of HeFH in adults. Adapted from Nordestgaard (21).

Criteria	Points
Family history	
First-degree relative with known premature ** CHD or first-degree relative with known LDL-C >95th percentile by age and gender for country	**1**
First-degree relative with tendon xanthoms and/or corneal arcus or child(ren) <18 years with LDL-C >95th percentile by age and gender for country	**2**
Clinical history	
Subject has premature ** CVD	**2**
Subject has premature ** cerebral or peripheral vascular disease	**1**
Physical examination	
Tendon xanthoma	**6**
Corneal arcus in a person <45 years	**4**
Biochemical results	
LDL-C >8.5 mmol/L	**8**
LDL-C 6.5 – 8.4 mmol/L	**5**
LDL-C 5.0 – 6.4 mmol/L	**3**
LDL-C 4.0 – 4.9 mmol/L	**1**
Molecular genetic testing (DNA analysis)	
Causative mutation shown in the LDLR, ApoB-100 or PCSK9 genes	**8**

* If the subjects scores > 8 points a "definite FH" diagnosis can be made, if the subject scores 6-8 points a probable diagnosis can be made and if the subject scores 3-5 point a possible diagnosis can be made.

** Premature: Men: <55 years, women: <60 years

A variety of approaches have been developed for diagnosing FH. A frequently used tool is the Dutch Lipid Clinic Network Criteria (**table 1**). Diagnosis of FH in adults is based on five criteria: (1) family history, (2) clinical history of premature CHD, (3) physical examination for xanthomas and corneal arcus, (4) elevated LDL-C measurements over time, (5) and/or a causative mutation detected by molecular genetics. If the children have a parent with FH and LDL-C >3.5 mmol/L, one should consider whether the child also has FH, as the risk is increased (21).

The Dutch Lipid Clinic Network Criteria should not be used in children. The optimal age for screening children is between 2 and 10 years, when it is optimal discrimination in cholesterol levels in children with or without FH. Screening is made on indication, and not performed on

the entire population. The reasonable age for initiating a low-fat diet is 2 years, and statin treatment is considered safe above age 8-10. Screening and initiating of treatment in early ages are considered beneficial (21).

A Norwegian study investigated 956 subjects with FH or Familial Defective ApoB-100 (FDB) during a 10 years period. In **figure 3** the relationship between TC (mmol/L) levels in FH/FDB patients without lipid-lowering therapy is plotted against age. The TC levels are increasing with age. It further shows TC years score for subjects who initiated lipid-lowering therapy at different decades and achieved a TC level of 5.4 mmol/L. The cholesterol-years score correlates with atherosclerosis severity in patients with HeFH (26). This study demonstrates the importance of early and adequate treatment.

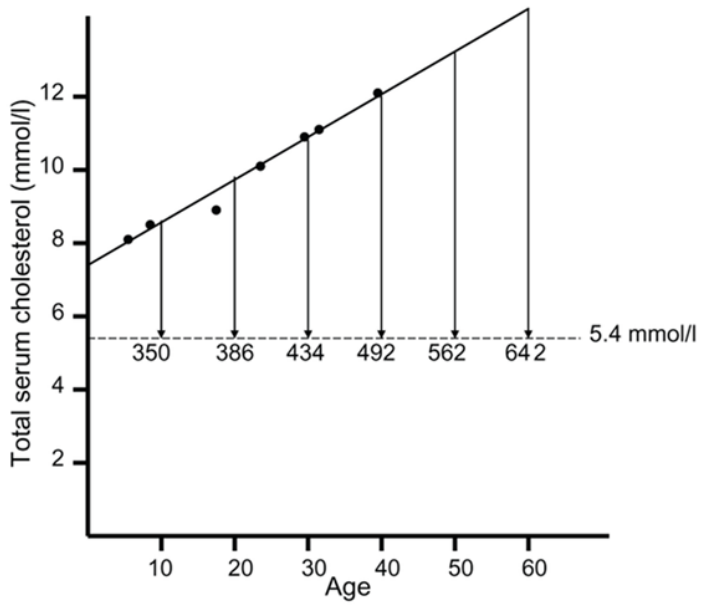

Figure 3. Cholesterol-years score in FH/FDB heterozygotes. Levels of total serum cholesterol in FH/FDB heterozygotes in different age groups before lipid-lowering therapy is started are plotted against age of the subjects. Adapted from: "Subjects with molecularly defined familial hypercholesterolemia or familial defective ApoB-100 are not being adequately treated" (26).

1.7.4 Clinical manifestations of FH

Most patients have no symptoms of hypercholesterolemia at time of diagnosis (24). The biggest difficulty is diagnosing the disorder in the asymptomatic population in order to commence early treatment (25).

Some clinical signs are associated with FH. These signs include xanthomas, xantelasms and premature CVD. Xantelasms and xanthomas are masses formed by clusters of macrophages and foam cells when they are present in subepithelial connective tissues or skin in tendon (11).

The presence of tendon xanthomas is virtually diagnostic for FH. Tendon xanthomas are most easily recognized within the extensor tendons such as in the extensor tendons on the dorsum of the hands and the Achilles tendons, where they cause thickenings and irregularities (27). Xantelasms are usually characterized by deposition of lipid in the cornea, leading to presenile corneal arcus (25). Premature corneal arcus is frequently seen in patients with HeFH. Corneal arcus is a lipid-enriched and mostly extracellular deposit which is accumulated in the stroma of the peripheral cornea (28).

The characteristic biochemical parameters of FH are elevated TC and LDL-C levels from birth. In addition, other lipid and non-lipid parameters are often measured in FH patients. HDL-C levels are usually slightly decreased, while levels of TG in plasma are often normal. Another lipoprotein abnormality is raised concentrations of Lp(a) (29).

Some patients with FH are diagnosed after a premature cardiovascular incidence. The premature CVD mainly occurs because of the accelerated atherosclerosis, resulting from an abnormally high LDL-C level (29).

1.7.5. Treatment of FH in children and adults

Treatment of FH involves drug treatment, dietary guidance and recommendations regarding lifestyle parameters.

Treatment goals

Table 2. Recommended LDL-C levels for FH patients. Adapted Nordestgaard (21).

	Recommended LDL-C
Children	<3.5 mmol/L
Adults	<2.5 mmol/L
Adults with CHD or diabetes	<1.8 mmol/L

The target goals are the same in HeFH and HoFH. Pediatric guidelines recommend lipid lowering drug therapy in children >10 years with LDL-C >4.9 mmol/L, or LDL-C >4.1 mmol/L if there is family history of premature CVD. It is also recommended if there exist at least two risk factors for CVD. Dietary modification should have been be tried without satisfactory results before initiating lipid-lowering drug therapy (30, 31).

Dietary and lifestyle recommendations in FH

Diet recommendations

Dietary treatment and a healthy lifestyle are recommended to all patients with FH in combination with lipid-lowering drug therapy (17). The main objectives of the nutritional advices are (1) to reduce the amount of foods and beverages with high cholesterol, saturated fat, and trans fat content, (2) to avoid overweight and maintain an ideal body weight, (3) no smoking and (4) regular physical activity (21, 32, 33). Achieving these advices may reduce the LDL-C levels and the risk of CVD.

Reduction of LDL-C is the major target of dietary treatment in FH patients. This is mainly accomplished by enhancing the activity of LDLR and by depressing liver synthesis of cholesterol. Both cholesterol and saturated fat down-regulate the LDLR, inhibit the removal of LDL-C from the bloodstream and increase the VLDL hepatic synthesis (32, 34, 35). Hence, avoiding foods containing a high level of cholesterol and saturated fat is essential in the dietary treatment of FH.

The major foods that are rich in saturated fats include those of animal origin, such as meat fats and dairy fats, and those of vegetable origin, such as coconut, palm kernel, palm oils and vegetable shortenings (27). Among the animal fats, the dairy fats are more hypercholesterolemic than the meat fats, due to its higher content of cholesterol-raising fatty

acids. The tropic oils (i.e. coconut, palm, and palm kernel oils) have higher content of saturated fatty acids than other vegetable oils (6).

Trans-fatty acids should be completely avoided as these are shown to increase LDL-C levels (6). The primary sources of trans-fatty acids are partially hydrogenated unsaturated fatty acids used to prepare certain commercial foods, such as fried and baked products (35).

Unsaturated fats are favorable compared to saturated fats (35). Unsaturated fatty acids, typically present in fish and vegetables, lower LDL-C levels when they are exchanged for saturated fatty acids in the diet. Hence, unsaturated fats may contribute to a healthier lipid profile (27). There are also low fat versions of certain products containing less fat (35).

An intake of approximately 2g/d of stanols or sterols has shown an LDL-C level reduction of about 10%. Enriching foods with stanols or sterols reduce intestinal absorption of cholesterol, and consequently lower serum cholesterol levels (36, 37).

According to National Cholesterol Education Program higher intake of soluble fiber (5-10 g/d) and soy protein produce stepwise reductions in LDL-C levels (1).

Patients with FH should be counseled in how the diet impacts their lipid values and risk of severe outcomes, and which dietary recommendations to follow. The recommendations include (17, 35) :

Table 3. Diet recommendations

Recommendations	**How to meet the recommendations**
Reduced intake of saturated fats and cholesterol	Total fat 25-35% of energy intake Saturated fatty acids < 7% of energy intake Dietary cholesterol <200 mg/d
Use of plant stanol or sterol esters	2 g/d
Use of soluble fiber	10-20 g/d

Even though diet therapy is well implemented in the treatment of FH, very few randomized controlled trials have been conducted on subjects with FH regarding diet. A Cochrane review on 11 randomized trials was published in 2010. The participants had various diets: (1) reduced total fat intake, (2) reduced intake of saturated fat, (3) reduced intake of cholesterol and (4) diet with increased amount of carbohydrates. It summarized that no conclusions could be

made about the effectiveness of cholesterol-lowering diet in patients with FH, due to lack of long-term trials with parallel group design. However, they found a significant lowering of plasma cholesterol when using plant sterols and/or stanols supplements (38). Several studies have investigated the TC and LDL-C lowering effects of using margarine or mayonnaise containing plant sterols and stanols. They found positive effects, and a maximal efficacy was achieved with an intake of about 2 g/d (39, 40).

A research team did two studies on healthy adults with hyperlipidemia. They investigated the effects of a dietary portfolio of cholesterol-lowering foods. Foods high in plant sterols, soy protein, viscous fibers and almonds were used in the studies. The LDL-C reduction was 28.6% and 12.8%, respectively, both significant (41, 42).

Although the effects of dietary intervention in treatment of FH are ambigous, there are defined diet recommendations for FH patients to follow.

Lifestyle recommendations

Physical activity

Regular physical activity (fast walking for 30 minutes five days a week) is one of the lifestyle advices of primary prevention of CHD (43).

Long-term observational studies investigating the benefits of exercise concluded with a significantly reduced risk of CHD in those who exercised regularly (44).

Cigarette smoking

American Heart Association strongly recommends eliminating use and exposure to all tobacco products (35). Cigarette smoking has been established as a powerful contributor to risk for CHD and other forms of CVD (1). Quit smoking has shown a risk reduction of $\geq$20% of CVD (6).

FH and statins

Statins are first choice treatment for all patients with FH (45). Early diagnostic and cholesterol-lowering treatment, primarily with statins, is essential for preventing premature

CHD. With satisfying statin treatment, studies have shown that subjects no longer have a risk of MI significantly different from that of the general population (45, 46).

Statins inhibit the enzyme HMG-CoA reductase in the liver and other tissues. Hence, statins reduces the synthesis of intracellular cholesterol in the liver. It causes induction of LDLR on the cell surface to hepatocytes. Increased number of LDLR further increases uptake and metabolism of cholesterol in the liver, and consequently decreases concentration of circulating TC, LDL-C and ApoB-100 levels (3, 27, 47).

A long-term cohort study investigated the lipid-lowering effects of two of the most used statins in FH patients. It found a reduction in LDL-C of 44% when initiating a Simvastatin mean dose of 33 mg, and a reduction in LDL-C of 49% when initiating a mean dose of 49 mg of Atorvastatin. It further showed a risk reduction of 76% for CHD compared to untreated FH patients (45).

Statin treatment in children

In Norway, statins are recommended as treatment in children with FH from the age of 8-10 years. Several studies have found reduced levels of TC, LDL-C and ApoB-100, and increased levels of HDL-C and ApoA-1, with use of statins in children. In addition, no harmful effects have been identified so far. However, long-term side effects can not be excluded due to lack of systematic long-term studies (48, 49).

FH and other medication

Other medication than statins may also be used if the patient is resistant to statin treatment, have side effects of statins, if the treatment goal is hard to reach etc.

Non-statin lipid-lowering drugs act through different mechanisms than statins, e.g. inhibit bile acid or cholesterol absorption. They act synergistic with statins. Used in combination, the LDL-C reduction may further increase. Ezetimibe, a cholesterol-absorption inhibitor, can be used in a combination with statin for further LDL-C lowering. Even in some HeFH patients a combination of high-dose statins and Ezetimibe is not enough to reduce LDL-C levels adequate. In this case, bile acids sequestrate and/or niacin can be further added (18).

1.8 Why this thesis?

To date, there is limited experience and knowledge about treatment of FH in children. Children and adolescents (<18 years) are vulnerable populations where adherence to treatment and understanding of the disease and lifestyle is every-day challenges, and the transition to an adult life is difficult. FH is a life-long disease, and it has to be properly monitored over several years.

The present master thesis is a systematic follow-up of previous study participants, and aims to provide knowledge and insight for future treatment and follow-up of FH patients.

2. Aims of the study

2.1 Study rationale

This thesis aims to identify effects of follow-up of previous participants involved in drug-trials and one plant sterol study at the Lipid Clinic, Oslo University Hospital when they were children (1999-2008). It examined a number of objective and subjective parameters, such as biochemical laboratory values, clinical manifestations and presentations, adherence of treatment, diet and lifestyle. Some parameters were, where appropriate, compared to recommendations, treatment goals or values at time of diagnosis.

2.2 Study objective

2.2.1 Specific aims of this thesis

Research Questions

i. To describe the following parameters
   - TC
   - LDL-C
   - HDL-C
   - TG
   - Lp(a)
   - BMI

ii. Objective parameters compared to the treatment goals
   - LDL-C

iii. Objective parameters in statin users versus non-statin users at follow-up compared to time of diagnosis
   - TC
   - LDL-C
   - HDL-C
   - TG

iv. Differences in objective parameters between genders at time of diagnosis and at time of follow-up
   - TC
   - LDL-C
   - ApoA-1, ApoB-100 and ApoB-100/ApoA-1 ratio

- HDL-C
- TG
- Possible explanations for differences?

v. Importance of outpatient control routines
- Association between last outpatient control and LDL-C level?
- Association between outpatient control frequency and LDL-C level?

vi. Dietary adherence and association to LDL-C levels
- Investigation according to SmartDiet questionnaire
- Adherence to dietary treatment
- LDL-C levels in participants with low score versus medium/high score

vii. Medication adherence
- Proportion using lipid-lowering drugs
- Common side effects and consequences
- Adherence to treatment
- Reasons for quitting medication and poor adherence

viii. Subjective experiences
- Participants` perceptions of their own health
- Participants` perceptions of being included in a study
- Participants` fears of CHD events

3. Subjects and methods

This follow-up project was approved by The Regional Committee of Medical Ethics (REK Vest), see **appendix 1**. Written informed consent was obtained from all participants. The data collection is based on blood samples, clinical manifestations, individual medical charts, SmartDiet questionnaire and a standardized interview. Blood samples were the only intervention in this project. Treatment was not initiated as a part of the study, but if there were indications for switching or initiating treatment this was implemented afterwards, and did not have any impact on the results. We also included measurements from a similar follow-up study in 2011, and added it to our original data.

3.1 Study design

3.1.1 Follow-up study

This was a systematic clinical, exploratory follow-up study. It included both retrospective and present measurements.

3.1.2 Substudy

Gisle Langslet at the Lipid Clinic had the overall responsibility for the project. He applied for Chief Physician leave of absence autumn 2013, to investigate FH children who had previously participated in clinical trials at the Lipid Clinic. It is planned to use the data in a doctoral dissertation, and this master thesis is a subset of this dissertation.

3.2 Subjects

3.2.1 Participants in the follow-up in 2013

Adults (>18 years) who participated in four clinical trials at the Lipid Clinic, three drug studies (study4, study5, study6) and one plant sterol study (study1), when they were children were asked to participate in this follow-up study. This comprised 41 participants in study1 (1999-2000) and 40 participants in study4, study5 and study6 (2005-2008) (50-53), totaling 81 participants. 8 persons participated in two of the studies and one person participated in three of the studies, leaving 71 individuals to be asked.

We have not been able to reach 10 of the 71 participants, three participants were reached by telephone once but not answered ever since, and another three participants did not meet for planned outpatient controls. The remaining 11 did not want to be included in the follow-up study. Two of these stayed in another country, while the other 9 did not have time or did not want to participate. Thus, 44 participants were recruited from the four parent studies. Of these 36 participants were interviewed at the Lipid Clinic, 7 were interviewed by telephone and one consented that we used medical chart information. Of the 44 participants interviewed, five did not have FH after all. All of them had previously participated in study1 and were excluded from our follow-up study.

In addition, a selection of participants not reached or not willing to participate in a similar follow-up study in 2011 was requested once again in 2013. Three consented to participate. An overview is illustrated in **appendix 2**.

3.2.2 Participants in the follow-up study in 2011

The similar follow-up study in 2011 recruited 25 of the 47 previous participants of the two statin studies in 2000 and 2001, Akid and Zink (study2 and study3) (54, 55). Data from these 25 participants were included in our follow-up.

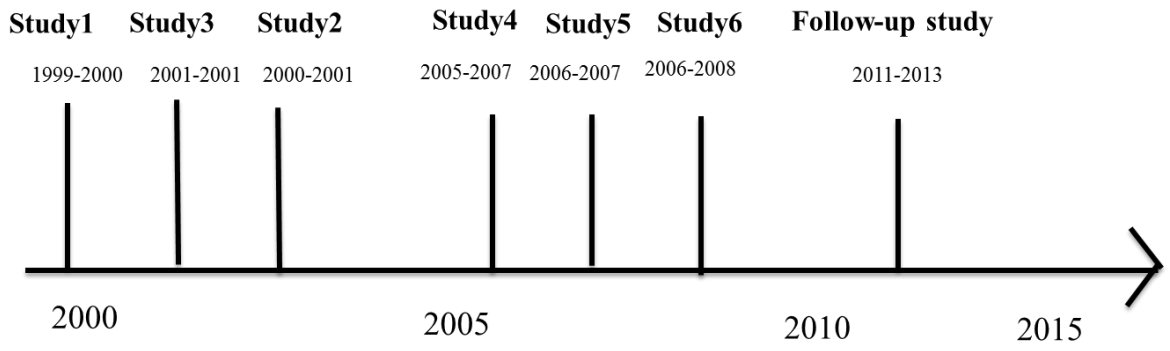

Figure 4. Timeline of parent studies

3.2.3 Participants participated in the follow-up in total

In total, there were 128 participants in the 6 parent studies of where our participants were recruited, shown in **table 4**. 8 persons participated in two of the parent studies and one person

participated in three of the studies, leaving 118 individuals to be asked. 67 of these were included in the study, illustrated in **figure 5**.

For those who participated in more than one of the parent studies the last study participation was used as reference.

Table 4. Overview of parent studies

Trial	Name in this follow-up	Year conducted	Participants
Plant Sterol	Study1	1999-2000	41
Akid	Study2	2000-2001	25
Zink	Study3	2000-2001	22
Welchol	Study4	2006-2007	9
Ezi/Simva	Study5	2005-2007	8
Pluto	Study6	2006-2008	23

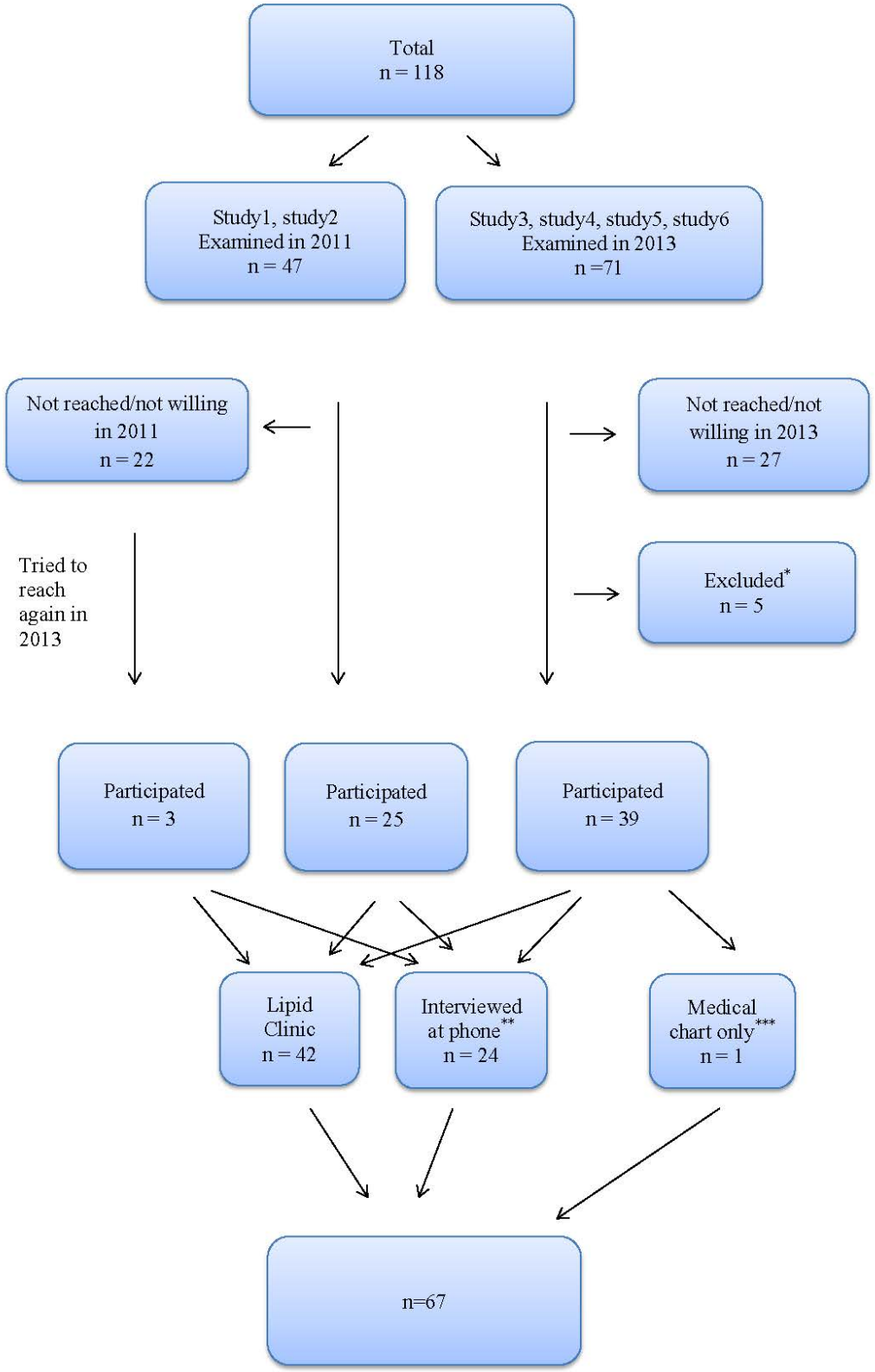

Figure 5. Flowchart of participation
* Did not have FH
** Did not have any outpatient control at the Lipid Clinic
*** Consented us to use information in medical chart

3.2.4 Inclusion and exclusion criteria

An overview of inclusion and exclusion criteria is shown in **table 5**.

Enrolled in this study were all subjects previous participated in 6 clinical trials (five drug trials and one plant sterol study) at the Lipid Clinic when they were children (<18years), with detected genetic or clinical FH and who signed written informed consent.

Participants previous participated in clinical trials at the Lipid Clinic when they were children (<18 years), but appeared not having FH after all, were excluded from the follow-up study.

Table 5. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Participated in clinical trial in 1999-2008 at the Lipid Clinic Genetic and/or clinical FH Signed written consent	Participated in clinical trial in 1999-2008, but turned out to not have FH

3.2.5 Missing values

In the follow-up study some missing values emerged among other due to incomplete medical records, inadequate answers from the participants and the fact that some participants only were interviewed by telephone and did not meet for outpatient controls. Missing values were not included in the percentage calculation in the result section, except in some analysis where including missing values provided a better overall picture. Therefore, almost all percentages presented in the results section are "valid percent" based on the participants where the data material is available.

3.3 Method

3.3.1 Recruitment

Persons participating in one or more of the 6 previous clinical trials mentioned above, were sent an invitation letter to participate with two copies of informed consent, see **appendix 3** (one copy for the participants themselves and one copy for the researchers), a SmartDiet questionnaire (**appendix 4**) and a prepaid "return envelope" per post. They were phoned 1-2 weeks afterwards and asked whether they wanted to participate in the study. If contact was not achieved, repeated phone calls were made and a "remainder" letter was sent, see

appendix 5. Potential participants were offered either an outpatient control along with the interview, or interview by telephone. If blood tests had not been performed for the last 6 months or a new treatment regimen was initiated, a new blood test was offered and a laboratory requisition was sent.

3.3.2 Biochemical parameters

At follow-up

If there were more than 6 months since the last blood sampling with lipid status was taken, participants were asked to give a blood test to make ordinary blood analysis at monitoring of individuals with FH: lipid status (TC, HDL-C, LDL- C, TG, Lp(a), ApoA-1 and ApoB-100), liver-, (ASAT and ALAT) kidney-, and thyroid tests, glucose status and muscle enzyme (CK). ApoB-100/ApoA-1 ratio was calculated from the collected blood samples. The participants were also asked for a new blood test if the treatment regimen was changed or if earlier blood samples did not contain any relevant results. The participants received a requisition in order to take a blood test, and the samples were conducted either locally or on the Lipid Clinic. Most of the blood tests were analyzed at the laboratory at Oslo University Hospital (OUS), Rikshospitalet, but could also have been drawn locally.

Standard procedures for patients not to eat or drink during the past 10 hours before the blood sampling were recommended (56).

Laboratory parameters at diagnosis

Biochemical parameters at diagnosis were collected from medical chart. The oldest values which existed in the medical chart were used. All values for lipid parameters such as TC, LDL-C, HDL-C and TG existed at diagnosis. In cases were LDL-C levels were missing and values for TC and HDL-C existed, Friedwalds formula was used to calculate the LDL-C levels.

Lp(a)

Values for Lp(a) were obtained from medical chart at anytime from time of diagnosis to follow-up in 59 participants. Usually there are small changes in Lp(a) values during lifetime. Hence, we decided only to use one value for each participant and not to compare Lp(a) values at different times.

3.3.3 Outpatient control

All participants enrolled in the follow-up were invited to an outpatient control with Chief Physician Gisle Langslet at the Lipid Clinic. The outpatient control included an assessment of the laboratory blood samples taken prior to the outpatient control, an assessment of the adherence of treatment, potential adverse effects of treatment regime since last outpatient control, as well as heart rate measurements and BP recordings.

When assessing frequency of outpatient controls, we included those participants at the Lipid Clinic or analogous institutions. If the participants had their first outpatient control somewhere outside the Lipid Clinic, the participants themselves reported time from the previous parent study participation to first outpatient control. As the Lipid Clinic do not have access to records outside Oslo University Hospital, some sporadic controls may have occurred at the general practitioner or other institutions without being included in this follow-up.

3.3.4 BP and pulse measurements

BP and heart rate were measured by Gisle Langslet in all participants who met up at the Lipid Clinic. It was measured using Welch Allyn 5300, automated blood pressure device (57). Measurements were conducted in the same manner in all participants. It was measured in a seated position after 5 minutes of rest, usually on the right arm**.**

No participants used anti-hypertensive medication, which could have influenced the measurements.

3.3.5 The interview

The interview collected information about age, gender, lipid values, illnesses in the past and drug use, possible side effects, information about treatment, outpatient control routines since participation in drug trials etc. They were also asked about their experience of having FH and how they would evaluate treatment and the outpatient controls they have received. The questions used in the interview are shown in **appendix 6**.

Interviews for previous participants in study2 and study3 (n = 25) were made in the summer months in 2011 by a medical student at the University of Oslo. Interviews for previous participants in study1, study4, study5 and study6, including three participants in study2 and study3 (n=42) were made by the master student in autumn 2013/January 2014. Questions

about treatment and side effects of treatment were asked by a Gisle Langslet, Chef Physician at the Lipid Clinic.

3.3.6 Anthropometric measurements

Body weight and height were measured by the master student of all participants who met at the Lipid Clinic. Measurements were performed in a similar manner in all participants. Among those who had an outpatient control at the Lipid Clinic, we both have self-reported and measured body weight and height, while among those who were interviewed by telephone we only have self-reported body weight and height.

Body weight was measured on an electronic body weight measurement apparatus called SOEHNLE S20, 2763. It was controlled and calibrated last time 14.06.2013 by the Norwegian Metrology Service. The patients were weighed without jackets and shoes, and stood in the center of the platform and looking straight ahead. Bodyweight was recorded to the nearest 0.1 kilogram.

Heights of the patients were measured with a manual height measurement scale of the brand Seca 222, attached to the wall. The measurements were made with the head in the Frankfurt plane, feet flat and with heels almost together, knees straight, heels buttocks, and shoulder blades in contact with the vertical surface of the wall (56).

Measured and self-reported weight and height were used to calculate body mass index (BMI) with the formula BMI = weight (kg)/height $(m)^2$ (56).

3.3.7 Collection of dietary data

Information about patients` diet and lifestyle were obtained using SmartDiet, a questionnaire with 26 questions developed by the Lipid Clinic, Oslo University Hospital, Rikshospitalet, shown in appendix 4.

The questionnaire consists of 21 questions about diet, where 14 of these made the basis of the total score. Each of the 14 scoring questions has three response categories for quality and specification of the quantity of the most commonly used foods. However, the quantity is not accurately recorded. Scores from each questionnaire were summarized. The maximum score

the subjects could achieve was 41 points. A total score of ≤27 is regarded as a low score, and indicates several improvements towards a more heart-friendly diet and lifestyle. A total score of 28-35 is a medium score, and the participants may obtain benefits of changing diet and lifestyle. A total score of ≥36 indicates a healthy diet.

The 21 questions concern the amount and frequency of average intake of foods of (1) "milk and yoghurt", (2) "cream, sour cream etc.", (3) "use of cheese", (4) “cold cuts”, (5) "meat for dinner", (6) "fish spread", (7) "fish for dinner", (8) "mayonnaise, remoulade and caviar", (9) "butter or margarine on bread", (10) "plant sterols", (11) "use of fats in food preparation", (12) "bread, crackers and other grain products", (13) "vegetables, fruits and berries", (14) "sweet topping and sweet drinks", (15) "chocolate, snacks, cakes, biscuits etc.", (16) "legumes", (17) "potato, rice and pasta", (18) "nuts, almonds, etc.", (19) "coffee", (20) "alcohol" and (21) “eggs.

The questionnaire also comprises five questions regarding lifestyle parameters: (1) “meal pattern”, (2) “height, weight and waist circumference”, (3) “smoking/chew tobacco”, (4) “physical activity” and (5) “dietary supplements”.

The form is particularly appropriate in the treatment and prevention of CVD and it has previously been validated against 7-day dietary records (58, 59).

Calculating the SmartDiet scores

In those participants who attended the Lipid Clinic the Chef Physician calculated the SmartDiet score manually. To verify the responses, the physician and the participants, went through the questionnaire together. The SmartDiet scores in the participants interviewed by telephone, who sent their responses by post, were calculated by the master student.

3.4 Statistical analysis

3.4.1 Preparation of data to be used in SPSS

The master student considered, coded and filled out information regarding variables of date of birth, age at diagnosis, age at parent study start, age at this follow-up, age when started cholesterol-lowering medication, history of cholesterol-lowering medication, biochemical values, SmartDiet scores and all subjective responses from the interview, in the statistical program SPSS. The information was gathered from the medical records, data from the parent studies, blood samples and the participants themselves.

3.4.2 Processing of data

All statistical analyses were performed using SPSS version 20.0 statistical package for Windows (SPSS, Inc., Chicago, Illinois, USA).

The level of statistical significance was set to $P < 0.05$ (2-sided). However, some of the results which were not statistically significant may be of clinical importance. This is further evaluated in the discussion section.

3.4.3 Presentation of data

Categorical variables

The results are presented as frequencies (%) for categorical variables. Categorical variables in the current study were outpatient control routines, LDL-C subgroups, BMI subgroups, lipid deposits, statin treatment, adherence and side effects of treatment, some of the lifestyle parameters, and most of the subjective parameters.

Differences between females and males in frequency of forgetting medication were tested with *Chi-square-test for Independence*. The results are illustrated in a 2 by 2 table. We used the value in the row of *Continuity correction*, which is recommended for 2 by 2 tables (60).

Continuous variables

To assess whether the continuous variables were normally distributed, *Histograms* and *Normal Q-Q plots* were evaluated for each variable. Most variables were not normally distributed, except all lipid parameters at time of diagnosis, TC at follow-up, and age at time of diagnosis, parent study start and follow-up.

The continuous data are presented as mean ± SD if the data were normally distributed and as median and range (min-max) if the data did not meet the assumptions for normal distribution. Differences between continuous data are tested with an *Independent Sample T-test* when normal distribution, *and Mann Whitney U test* when no normal distribution.

Wilcoxon Signed Rank Test was used to compare lipid parameters at time of diagnosis and at follow-up, both when stratified for statin/non-statin users and females/males. The results were presented in median differences and p-values.

4. Results

4.1 Overview of the study population

Study population characteristics are summarized in **table 6.** The final sample consisted of 67 participants, 29 females and 38 males. Average age at diagnosis was 8.1 (± 3.6) years. The average age of the participants in this follow-up was 25 (± 3.0) years, with a range from 19-30 years.

64 participants were verified by genetic testing. Only three were not genetic tested, but diagnosed clinically. 21 different mutations in the LDLR gene were found. The four most common mutations, FH-Elverum, C210G, FH-Svartor and FH-Gujerat, occurred in 41 (61.3%) of the subjects.

9 (13.4%) participants had parents with CHD and 39 (58.2%) had parents or grandparents with CHD.

Table 6. Age of the study population

Characteristics	Female	Male	Total
n [1]	29 (43.3%)	38 (56.7%)	67 (100 %)
Age at diagnosis (y) (SD)	7.7 (2.8)	8.5 (4.2)	8.1 (3.6)
Min-max	3.0-14	1.0-17	1.0-17
Age at parent study-start (y) (SD)	14 (2.4)	14(1.9)	14 (2.1)
Min-max	8.2-18	9.9-17	8.2-18
Age at this follow-up study (y) (SD)	25 (2.6)	24 (3.1)	25 (3.0)
Min-max	21-30	19-30	19-30

Data are given as mean and (SD) or number of participants and (%)
[1] n indicates number of individuals (%)

An overview of participation in the parent studies among the subjects in our follow-up is shown in **appendix 7**. Most subjects had participated in one previous parent study 59 (88.1%), while 7 (10.5%) had participated in two previous studies and one participant (1.5%) had participated in three previous clinical trials at the Lipid Clinic. Shown in **appendix 8,** more than 70% of the study population was included in the parent studies because their parents decided, and participants agreed. One participant (1.5%) was included against its will.

Main reasons for participation were the thought of better treatment and monitoring of the disease (54.5%), scientific reasons (16.7%), and both of these.

A great majority (90.8%) of the participants found it positive to have been included in the study. Approximately two third reported close monitoring, including dietary advices, as the most common positive responses. Approximately 10% of the participants reported that they had negative experiences of being involved in the study among other due to discomfort during blood sample drawing (appendix 8).

4.2 Outpatient control routines

Outpatient control routines after participation in the parent study are shown in **table 7a**. There were no significant differences in outpatient control frequency the past 10 years between females and males (P = 1.0). After participation in parent studies almost all subjects (94.0%) had their first outpatient control at the Lipid Clinic, and as many as 58 (86.6%) have had every outpatient control at the Lipid Clinic. 46 (68.7%) participants had their first outpatient control within two years after the parent studies, while in three (4.5%) participants it took more than five years before the first outpatient control.

50 (74.6%) subjects have been to outpatient control more often than every second year the past 10 years, while 7 (10.5%) subjects have been to outpatient control less than every third year.

The median number of years since last outpatient control was 1.5 (0.0-6.5) years (**Table7b).** No significant differences were found in females and males (P = 0.79). Median years since ended the parent studies to participation in this current follow-up were 10 years.

Table 7a. Outpatient control routines

Characteristics	n [1] (%)
First outpatient control after parent study participation	
Lipid Clinic	63 (94.0%)
General practitioner	3 (4.5%)
Another place	1 (1.5%)
Changed place for outpatient control after the parent study	
No	58 (86.6%)
Yes	9 (13.4%)
If changed, what is the reason	
N/A*	58 (86.6%)
More practical with local outpatient control	5 (7.5%)
Have not been followed up at LK/too long to wait for outpatient control	2 (3.0%)
Do not know	2 (3.0%)
Years before outpatient control after participation in the parent study	
≤1 year	13 (19.4%)
>1 - ≤2 years	33 (49.3%)
>2 - ≤3 years	18 (26.9%)
>3 - ≤5 years	0 (0.0%)
>5 years	3 (4.5%)
No follow-up	
Frequency of outpatient control the past 10 years	
≤1 year intervals	13 (19.4%)
>1 - ≤2 years intervals **	37 (55.2%)
>2 - ≤3 years intervals	10 (14.9%)
>3 - ≤5 years intervals	5 (7.5%)
>5 years intervals	2 (3.0%)

Data are given in n (%)
[1] n indicates number of individuals
* N/A values are included in the analysis due to the great number of participants in this group
** The participants who were at outpatient control every second year are in this category
N/A = not applicable

Table 7b. Outpatient control routines in years

Characteristics	n [1]	Years
Years since last outpatient control	61	1.5
Min-max		0.0-6.5
Years since ended study to participation in follow-up	67	10
Min-max		5.4-14

Data are given as median (min-max)
[1] n indicates number of individuals

4.3 Biochemical parameters

An overview of lipid parameters at time of diagnosis and at follow-up is shown in **table 8a.**

Median TC level at diagnosis and follow-up in statin users was 8.5 mmol/L and 5.1 mmol/L, respectively, a significant reduction from time of diagnosis to follow-up (P <0.001) of 40%. In non-statin users median TC level at diagnosis and at follow-up was 8.4 mmol/L and 7.5 mmol/L, respectively, a non-significant reduction (P = 0.10). In statin users, median LDL-C level at diagnosis was 6.6 mmol/L and 3.3 mmol/L at follow-up. This was a significant reduction (P <0.001) of 50%. In non-statin users' median LDL-C levels at diagnosis and at follow-up were 6.8 mmol/L and 5.8 mmol/L, respectively. The reduction was not significant (P = 0.55).

We also found a significant difference between median LDL-C level in statin-users vs. non-statin users of 2.5 mmol/L (P <0.001). Although the median LDL-C level is lower in statin users than in non-statin users, the treatment goal of LDL-C $\leq$2.5 mmol/L is not achieved (21).

The reduction in females and males in TC level was 43% and 24%, respectively, P <0.001 (**table 8b**). In LDL-C level the reduction in females and males was 55% and 23%, respectively (P <0.001)

The differences between genders are illustrated in table 8b**.** Females had significantly higher (P = 0.016) TC level at diagnosis than males. This was also applicable in LDL-C levels at diagnosis were woman had a significantly higher (P<0.001) LDL-C level than men (7.5 mmol/L vs. 6.1 mmol/L). However, this difference has reversed at follow-up were women had a numerical lower TC and LDL-C level than men. Median TC level in females was 5.4 mmol/L versus 6.1 mmol/L in males. The difference was 0.7 mmol/L, which was not significant (P = 0.24). The median LDL-C value was 3.4 mmol/L in females, while the median value among males was 4.7 mmol/L, a difference of 1.3 mmol/L. The difference was not statistically significant (P = 0.064).

The values for HDL-C and TG for females and males are within the reference range of medical department of Rikshospitalet University Hospital at the time of diagnosis and follow-up (61).

In total, the lipid profile is more beneficial at follow-up than at time of diagnosis.

The median TC and LDL-C level at follow-up for the study population in total are illustrated in **table 8c**. The values were 5.7 mmol/L and 4.0 mmol/L, respectively.

Table 8a. Lipid levels at diagnosis and follow-up

	At diagnosis		At follow-up		P [2]	
	Statin use [*]	**Non-statin use** [**]	**Statin use** [*]	**Non-statin use** [**]	**Statin use** [*]	**Non-statin use** [**]
n [1]	48	19	47	18		
TC (mmol/L)	8.5	8.4	5.1	7.5	**<0.001**	0.10
Min-max	5.5-12	6.6-10	3.6-8.5	6.0-12	-	-
Reduction [***]	-	-	(-40%) [****]	(-11%)	-	-
LDL-C (mmol/L)	6.6	6.8	3.3	5.8	**<0.001**	0.55
Min-max	4.0-10	5.0-8.5	2.0-6.8	4.0-9.8	-	-
Reduction [***]	-	-	(-50%) [****]	(-15%)	-	-
HDL-C (mmol/L)	1.3	1.3	1.4	1.3	**0.021**	0.94
Min-max	0.7-2.0	0.8-2.3	0.8-2.5	0.8-2.2	-	-
TG (mmol/L)	0.75	0.76	0.70	0.90	0.23	**0.05**
Min-max	0.1-2.9	0.4-1.8	0.4-2.3	0.6-1.9	-	-

Data are given in median (min-max) and reduction in %

[1] n indicates number of individuals

[2] *Wilcoxon Signed Rank Test*, comparison of lipid parameters at time of diagnosis versus at follow-up, statistically significant when P <0.05.

[*] Used statins at follow-up

[**] Did not use statins at follow-up

[***] Reduction in LDL-C (%) from time of diagnosis to follow-up

[****] *Wilcoxon Sign Rank Test*, statistically significant reduction P <0.001.

TC = total cholesterol, LDL-C = low-density cholesterol, HDL-C = high-density cholesterol, TG = triglycerides

Two blood (n = 2) samples are missing at follow-up

Table 8b. Differences in lipid parameters between females and males

	At diagnosis , female	At diagnosis, male	Median differences [1]	P [2]	At follow-up , female	At follow-up, male	Median differences [1]	P [2]
n	29	38			27	38		
TC (mmol/L)	9.4	8.0	1.4	**0.016**	5.4	6.1	0.70	0.24
Reduction [*]	-	-	-	-	(-43%) [**]	(-24%) [**]	-	-
Min-max	6.5-12	5.5-11	-	-	3.9-9.5	3.6-12	-	-
LDL-C (mmol/L)	7.5	6.1	1.4	**0.001**	3.4	4.7	1.3	0.064
Reduction [*]	-	-	-	-	(-55%) [**]	(-23%) [**]	-	-
Min-max	4.8-10	4.0-8.3	-	-	2.0-7.4	2.0-9.8	-	-
HDL-C (mmol/L)	1.3	1.2	0.10	0.53	1.5	1.2	0.3	**<0.001**
Min-max	0.7-2.3	0.8-2.0	-	-	1.0-2.5	0.8-1.8	-	-
TG (mmol/L)	0.82	0.69	0.13	**0.040**	0.70	0.90	0.2	0.070
Min-max	0.3-2.9	0.1-1.8	-	-	0.4-2.3	0.4-2.0	-	-

Data are given as median (min-max) and reduction (%)

[1] Median differences between females and males at time of diagnosis

[2] *Mann-Whitney U Test*, differences between genders, statistically significance when P <0.05

[*] Reduction in % from time of diagnosis to follow-up in females and males

[**] *Wilcoxon Sign Rank Test,* statistically significant reduction, P <0.001.

TC = total cholesterol, LDL-C = low-density cholesterol, HDL-C = high-density cholesterol, TG = triglycerides

Table 8c. TC and LDL-C levels at follow-up in the total study population

	At follow-up [2]
n [1]	65
TC (mmol/L)	5.7
Min-max	3.6-12
LDL-C (mmol/L)	4.0
Min -max	2.0-9.8

Data are given as median (min-max)
[1] n indicates number of participants

LDL-C subgroups, stratified in statin users (n=47) and non-statin users (n=18), based on the LDL-C level at time of follow-up are shown in **table 9**. 6 (12.8%) of the current statin users achieved the treatment goal of LDL-C ≤2.5 mmol/L, 23 (48.9%) of the statin users had a LDL-C level between 2.5 mmol/L and 3.5 mmol/L. None (0.0%) of the non-statin users had a LDL-C level of ≤3.5mmol/L. 11 (23.4%) of the statin users, and as much as 16 (88.9%) of the non-statin users, had a LDL-C level above 4.5 mmol/L.

Table 9. LDL-C subgroups

LDL-C	**n (%)** [2] **Statin users**	**n (%) Non-statin users**
n [1]	47	18
LDL-C ≤2.5 mmol/L	**6 (12.8%)**	**0 (0.0%)**
LDL-C ≤3.5 mmol/L	**29 (61.7%)**	**0 (0.0%)**
LDL-C ≤4.5 mmol/L	36 (76.6%)	2 (11.1%)
LDL-C >4.5 mmol/L	11 (23.4%)	16 (88.9%)

Data are given in n (%)
[1] n indicates number of individuals
[2] Cumulative percent ≤4.5 mmol/L, valid percent >4.5 mmol/L
LDL-C = low-density cholesterol

As shown in **table 10,** the median values of ApoA-1 and ApoB-100 at follow-up were within the reference range for both males and females, though in the upper layer in ApoB-100 for males (61). Females had a higher ApoA-1 level (P = 0.002) and a lower ApoB-100 level (P = 0.050) and ApoB-100/ApoA-1 ratio (P = 0.001) than males. The values of ApoA-1 and ApoB-100 at time of diagnosis were not included in this follow-up.

Table 10. ApoA-1 and ApoB-100 levels at follow-up

Characteristics	At follow-up, female	At follow-up, male	At follow-up, total	P [2]
n [1]	26	38	64	
ApoA-1 (g/L) [*]	1.5	1.3	1.4	**0.002**
Min- max	1.1-2.0	0.9-1.8	0.9-2.0	
ApoB-100 (g/L)[**]	1.0	1.3	1.2	**0.050**
Min-max	0.6-1.8	0.5-2.3	0.5-2.3	
ApoB-100/ApoA1	0.67	1.0	0.85	**0.001**
Min-max	0.3-1.4	0.4-2.3	0.3-2.3	

Data are given as median and min-max values
[1] n indicates number of subjects
[2] *Mann-Whitney U Test*, statistically significant when P <0.05.
[*] Normal range: **Female:** 1, 1–2, 3 g/L, **Male:** 1, 0–2, 0 g/L
[**] Normal range: 0, 5–1, 3 g/L
ApoA-1 = Apolipoprotein A-1, ApoB-100 = Apolipoprotein B-100, ApoA-1/ApoB-100 = Apoliprotein A-1/B-100

Shown In **table 11**, the median level of Lp(a) were 269 mmol/L.

There were no significant differences in Lp(a) between genders (P = 0.077). 15 (25.4%) of the participants had a Lp(a) value ≤100 mg/L, 28 (47.5%) had a Lp(a) value ≥300mg/L, while 12 (28.8%) of the participants had a Lp(a) in the range of 500 – 999 mgl/L and five (8.5%) of the participants had a Lp(a) value ≥1000 mg/L.

There is no significant difference in Lp(a) levels according to CHD history in parents and/or grandparents (P = 0.67) between the participants, neither when Lp(a) ≥300 mg/L (P = 0.77), nor when Lp(a) ≥500mg/L (P = 1.0), data not shown.

Table 11. Lp(a) levels at anytime

Characteristics	Total
n [1]	59
Lp(a) at any time (mg/L)	269
Min-max	14.0-3360

Data are given as median (min-max)
[1] n indicates number of individuals
Lp(a) = Lipoprotein (a)

The median values of laboratory parameters such as ASAT, ALAT, CK, glucose and HbA1c are generally within the reference range. One non-statin user had moderately elevated CK,

while another non-statin user had slightly elevated CK levels. One participant had slightly elevated ASAT. Another two participants had slightly elevated ALAT (61).

4.4 LDL-C level according to outpatient control frequency, years since last outpatient control and family history of CVD

Median LDL-C level of those followed up every second year or more often the last 10 years was lower (3.6 mmol/L) than the LDL-C levels of those followed up less frequently than every two years (4.9 mmol/L). However, the difference was not significant, P = 0.069 (**table 12a**).

A significant (P = 0.044) lower median LDL-C level were discovered in those who had been to outpatient control two years or less before the interview (3.8 mmol/L), compared to the participants who have been to last outpatient control more than two years before the interview (5.0 mmol/L), illustrated in **table 12b**.

Table 12a. LDL-C levels according to outpatient control frequency

Characteristics	**Outpatient control frequency ***		**P** [2]
	Every two years or more often	**Less than every two years**	
n [1]	48	17	
LDL-C levels (mmol/L) at follow-up	3.6 (2.0-7.5)	4.9 (2.7-9.8)	0.069

Data are given as median (min-max)
[1] n indicates number of individuals
[1] *Mann-Whitney U Test*, statistically significance when P <0.05
[*] The past 10 years

Table 12b. LDL-C levels according to years since last outpatient control

Characteristics	**Years since last consultation**		**P** [2]
	Two years or less	**More than two years**	
n [1]	41	19	
LDL-C levels (mmol/L)at follow-up	3.8 (2.0-7.4)	5.0 (2.6-9.8)	**0.044**

Data are given as median (min-max)
[1] n indicates number of individuals
[2] *Mann-Whitney U Test*, statistically significant when P <0.05
LDL-C = low-density lipoprotein cholesterol

LDL-C level according to family history of CVD in parents and grandparents is shown in **table 13.** Participants having parents or grandparents with CVD events, had no significantly higher LDL-C level (4.2 mmol/L) than the participants not having parents or grandparents with CVD events (3.8 mmol/L), P = 0.85.

Table 13. LDL-C levels according to family history of CVD

Characteristics	**CVD in parents or grandparents**		**P** [2]
	No	**Yes**	
n [1]	27	38	
LDL-C levels at follow-up (mmol/L)	3.8 (2.0-7.5)	4.2 (2.0-9.8)	0.85

Data are given as median (min-max)
[1] n indicates number of individuals
[2] *Mann-Whitney U Test*, statistically significant when P <0.05
LDL-C = low-density lipoprotein cholesterol

4.5 Clinical findings

Clinical findings in the study population at time of follow-up are illustrated in **table 14**. The participants were within the normal range of BMI both for measured and self-reported values (56). Although more than 60% of the study population was within the normal range of BMI of 18.5-25.0 (self-reported values), slightly less than one third had a BMI above 25, and is per definition overweight.

As expected in a young study population, most of the participants had normal BP values (93.7%). Only 3 (7.3%) had slightly elevated BP. No one used anti-hypersensitive medication.

Lipid deposits were detected in 6 (9.2%) subjects, while 9 (13.8%) subjects interviewed by telephone did not know whether they had lipid deposits or not.

Table 14. Physical examination at follow-up

Characteristics	n [1]	Median / n (%)
Measured BMI	31	23.4
Min-max		17.8-37.9
Self-reported BMI	56	23.2
Min-max		16.3-35.3
<18.5		2 (3.6%) [2]
18.5-25.0		36 (64.3%)
>25.0-30.0		12 (21.4%)
>30.0		6 (10.7%)
Systolic BP (mmHg)	41	123
Min-max		102-144
Diastolic BP (mmHg)	41	72
Min-max		51-96
High BP [3] (%)	41	
Yes		3 (7.3%) [2]
No		38 (92.7%)
Lipid deposit [4]	65	
Yes		6 (9.2%) [2]
No		50 (76.9%)
Do not know		9 (13.8%)

Data are given as median (min-max) and n (%)
[1] n indicates number of participants
[2] Data are given in valid percent
[3] High blood pressure = systolic > 140 mmHg or diastolic >90 mmHg
[4] Lipid deposit: Arcus cornea and/or xanthomas, data from medical records.
BMI = body mass index, kg/m^2 (self-reported and measured), BP = blood pressure

4.6 Treatment and side effects

Shown in **table 15a,** median number of years the participants had used statins were 6.6 years (except blinded study period), with a range from 0 to 17.6 years. Among the participants who started treatment, 43 (64.2%) of them started with statins.

19 persons (28.4%) did not use lipid-lowering drugs at the time of follow-up. One person had not been given a prescription due to uncertain FH diagnosis. Another person had got a prescription, but never started the medication. The remaining 17 had used statins previously. When investigating reasons for subjects not using statins, the following factors are listed: side effects, poor routines, lack of motivation, running out of prescription and skepticism about

using drugs. There were no statistically difference in females and males regarding use of statins at follow-up (P = 1.0).

Table 15a. History of medical treatment

Characteristics	n (%)
n [1]	67
Age started with cholesterol-lowering drugs (y)	15
Min-max	5.0-25
First cholesterol-lowering medication	
Statin	43 (64.2%)
Resin	22 (32.8%)
Never used medication	2 (3.0%)
Statin treatment, years in total [2] (y)	6.6 [*]
Min-max	0.0-18
Use of statin today	
Yes	48 (71.6%)
No	19 (28.4%)
If not what is the reason	
N/A	48
Run out of pills, have not renewed prescription	4 (21.1%) [3]
Sporadic use, can not remember / forget	4 (21.2%)
Pregnancy or lactation	2 (10.5%)
Side effects	5 (31.6%)
Skeptical of use of medicine because of side effects	1 (5.3%)
Uncertain diagnosis	1 (5.3%)
Have been prescribed, not initiated	1 (5.3%)

Data are given as median (min-max) and n (%)
[1] n indicates number of individuals.
[2] Except periods with blinded study medication
[3] Data are given in valid percent
[*] n=65, two (n=2) have not ever used medication
N/A = not applicable

A significant difference (P = 0.021) were found between current statin users versus non-statin users when statistically tested against number of years since last outpatient control, seen in **table 15b**.

Table 15b. Association between use of statins and last outpatient control

Characteristics	Use of statins		P [2]
	Yes	No	
n [1]	42	19	
Years since last outpatient control	1.4 (0.0-6.5)	2.2 (0.08-5.9)	**0.021**

Data are given as median (min-max)
[1] n indicates number of individuals
[2] *Mann-Whitney U* Test, statistically significant when P <0.0

Among those who used medication, 31 (64.6%) used Atorvastatin (Lipitor) and additionally 6 (12.5%) used Atorvastatin and Ezetimibe (10mg) in combination, **table 16**. Less commonly used statins were Rosuvastatin and Simvastain.

Table 16. Type of medication

If using medication, type	n (%) [1]	Drug dose, mg [2]
N/A	19	
Simvastatin	4 (8.3%)	40
Atorvastatin	31 (64.6%)	40
Rosuvastatin	5 (10.4%)	40
Pravastatin + Ezetimibe	1 (2.1%)	40+10
Atorvastatin + Ezetimibe	6 (12.5%)	60+10
Rosuvastatin + Ezetimibe	1 (2.1%)	20+10

Data are given in median and n (valid percent)
[1] n indicates number of individuals
[2] Median dosages (mg/day)
N/A = not applicable

24 (40.7%) participants take their medicine every day, while as much as 17 (28.9%) responded to forget the medicine once a week or more often (**table 17a**). There was no difference between the genders in frequency of forgetting to take their medicine (P = 0.88), shown in **table 17b**. The far most common reason for forgetting their medicine was irregularities/poor routines (50%).

Table 17a. Adherence to medical treatment

Characteristics	n [1] (%)
Do you forget to take the medicine?	
N/A	7
Never	24 (40.7%)
1-2 times a month	16 (27.1%)
Once a week	9 (15.3%)
More often than once a week	8 (13.6%)
Yes, periodically	2 (3.4%)
What are the reasons for poor adherence?	
N/A	31
Irregularities/poor routines	17 (50.0%)
Traveling	7 (20.6%)
Run out / missing prescription	1 (2.9%)
Do not know	1 (2.9%)
Other	8 (23.5%)

Data are given as n (valid percent)
[1] n indicates number of individuals
N/A = not applicable

Table 17b. Adherence to medical treatment among genders

		Females	Males	P [1]
Forget medication [*]	1-2 times a month or never	19 (73.1 %)	21 (67.7%)	0.88
	Once a week or more often [**]	7 (26.9%)	10 (32.3%)	

Data are given in n (%), n indicates number of participants
[1] *Chi-Square Test*, statistically significant when P <0.05
[*] Of the participants using medication
[**] "Yes, periodically" (n = 3) is taken out of the data material for this analysis.

More than 35% of the study population has experienced side effects due to lipid lowering medication. The gastrointestinal side effects occurred most frequently (n = 12, 46.2%), followed by musculoskeletal complaints.

Among participants reporting side effects more than two thirds reported that it affected their quality of life to some degree. However, there were only three (11.5%) participants where the side effects affected the quality of life in a great extent.

Among the study population reporting side effects 19 (73.1 %) changed or stopped using their medication, and 7 of them stopped permanently.

Table 18. Side effects of medical treatment

Characteristics	n [1] (%)
Side effects	
No	39 (58.2%)
Yes	24 (35.8%)
Maybe	2 (3.0%)
Do not know/ Have not used medication ever	2 (3.0%)
If side effects, which type	
N/A	41
Gastrointestinal	12 (46.2%)
Muscle or joint pain	5 (19.2%)
Headache	1 (3.8%)
Fatigue	0 (0.0%)
Gastrointestinal + headache	2 (7.7%)
Gastrointestinal + fatigue	1 (3.8%)
Muscle pain + headache	1 (3.8%)
Muscle pain + fatigue	3 (11.5%)
Other	1 (3.8%)
If you ever have had side effects how has it affected your quality of life?	
N/A	41
Nothing	5 (19.2%)
A little	18 (69.2%)
Much	3 (11.5%)
If side effects, how has it affected your treatment?	
N/A	41
Not affected	6 (23.1%)
Slightly affected	1 (3.8%)
Discontinuation of treatment/change of treatment	19 (73.1%)

Data are given in n (valid percent)
[1] n indicates number of individuals
N/A = not applicable

4.7 Diet and lifestyle

SmartDiet score was gathered in 64 participants, where the median score was 32.5 points of a total maximum score of 41 points. This was in the range of a medium score level.

The median level in total SmartDiet score in females and males was 34.0 and 31.5, respectively. However, the difference was not significant (P = 0.075).

The median score for milk and dairy products was high, which means that they had a high consume of low-fat dairy products. The same was applicable for intake of meat and meat products during a week, while they had a low intake of fish and fish products and therefore a lower score. For vegetables and fruits the median score was two out of a maximum of three points. Less than one quarter of the participants used omega-3 supplementation and plant sterols at follow-up.

Median LDL-C in participants with a medium and high SmartDiet score (n = 56) of >27 was 3.6 mmol/L compared to 4.9 mmol/L in participants with low SmartDiet score (n = 8) of $\leq$27. However, the difference was not significant (P = 0.70).

Table 19. SmartDiet questionnaire

Characteristics	n [1]	Median
Total SmartDiet score at study visit (of maximum 41 points)	64	32.5
Min-max		19.0-39.0
High [2]		9 (14.1%) [*]
Medium [3]		47 (73.4%)
Low [4]		8 (12.5%)
Consumption of cheese on the bread, cooking, on the pizza ect. [*]	62	2.0
Consumption of milk and dairy products [**]	62	5.0
Consumption of fish and fish products during one week [**]	62	3.5
Consumption of meat and meat products during one week [**]	61	6.0
Consumption of fruit and vegetables during one week [*]	62	2.0
Consumption of bread and cereals during one week [*]	61	3.0
Use of omega 3 supplementation (%)[***]	64	
Yes		18 (28.1%)
No		46 (71.9%)
Use of plant sterols (%) [***]	62	
Yes		18 (29.0%)
No		44 (71.0%)

Data are given as median and max-min, or n (%)
[1] n indicates number of individuals
[2] High SmartDiet score means a score of 36 points or more
[3] Medium SmartDiet score means a score between 28 and 35 points
[4] Low SmartDiet score means a score of 27 or lower.
[*] Maximum 3 points
[**] Maximum 6 points
[***] Used valid percent

In **table 20**, hours of exercising per week are shown. In median the participants used 1.0 hour a week training body strength and 2.5 hours on endurances. Within the study population there was a great range between the participants; from the participants who did not use any time exercising, to one participant who used more than 20 hours a week.

Most of the study population consumed alcohol during a week. Almost 70% consumed 1-7 units' alcohol during a week, while a small group of the study population (13.4%) reported that they never consumed alcohol.

46 (69.7%) had never used tobacco, only five (7.6%) smoked daily, while 7.6% reported themselves as "party-smokers". The participants who previously had smoked or smoked at

follow-up had in median smoked for approximately 6 years. A greater number used chew tobacco, with a total of 18 (26.9%) in the study population. In median they had used "Swedish snuff" for almost 5 years.

Table 20. Lifestyle – Physical activity, alcohol consumption and tobacco use

Characteristics, n=66	**Median/ n (%)**
Exercise	
Hours strength, per week	1.0
Min-max	0.0-7.5
Hours endurances, per week	2.5
Min- max	0.0-20
Alcohol, units per week	
0	9 (13.4%)
1-7	46 (86.7%)
8-14	9 (13.4%)
15 units or more	2 (3.0%)
Tobacco use	
No/never	46 (69.7%)
Yes	5 (7.6%)
"Party smoker"/rarely [2]	5 (7.6%)
Have quitted	10 (15.2%)
If yes, number of years smoked, (n=19 [3])	6.0
Min-max	0.2-12
"Swedish snuff" use	
Yes	18 (26.9%)
No	44 (65.7%)
Occasionally	1 (1.5%)
Have quitted	3 (4.5%)
If yes, number of years used "Swedish snuff"	4.75
Min-max	0.1-14

Data is given as median and min-max or n (valid percent)
[1] n indicates number of individuals
[2] Definition "party-smoker": 1-2 times a week – 1 times a month
[3] The last one does not remember how many years he/she has smoked.

4.8 Subjective evaluations of own health

There are just as many participants that are satisfied with their cholesterol levels (46%), as there are participants that are dissatisfied (46%), illustrated in **table 21a.**

Table 21a. Subjective evaluation of cholesterol levels

Are you satisfied with your cholesterol values?	n [1](%)
Agree fully	8 (13.1%)
Agree partly	20 (32.8%)
Neither agree or disagree	5 (8.2%)
Disagree partly	11 (18.0%)
Disagree fully	17 (27.9%)

Data are given as n (valid percent)
[1] n indicates number of individuals

More than 27 (40%) of the study population believed that their heath was better than the average, shown in **table 21b**. Almost half of the study population (45.5%) was worried about having a CHD event, and 53 (80.3%) of the participants believed that their treatment will prevent them from having a CHD event.

Table 21b. Subjective evaluation of own health

Characteristics	n [1] (%)
How do you consider your health?	
Better than average	27 (40.9%)
Average	34 (51.5%)
Worse than average	5 (7.6%)
Are you worried about having a CHD event because of FH?	
Agree fully	6 (9.1%)
Agree partly	24 (36.4%)
Neither agree or disagree	7 (10.6%)
Disagree partly	13 (19.7%)
Disagree fully	16 (24.2%)
Do you rust that your treatment will prevent you from having a CHD event?	
Agree fully	19 (28.8%)
Agree partly	34 (51.5%)
Nether agree or disagree	5 (7.6%)
Disagree partly	5 (7.6%)
Disagree fully	3 (4.5%)
Are you afraid that one of your parents who has FH will have a CHD event (again)?	
Agree fully	26 (40.0%)
Agree partly	16 (24.6%)
Neither agree or disagree	5 (7.7%)
Disagree partly	6 (9.2%)
Disagree fully	12 (18.5%)
Are you anxious that your children can inherit FH from you?	
Agree fully	20 (30.3%)
Agree partly	22 (33.8%)
Neither agree or disagree	5 (7.7%)
Disagree partly	8 (12.3%)
Disagree fully	10 (15.4%)

Data are given in n (valid percent)
[1] n indicates number of individuals

5. Discussion

In this thesis we did a follow-up of participants in 6 randomized clinical trials at the Lipid Clinic from 1999 to 2006. It involves cross-sectional measurements and retrospective measurements of clinical and biochemical parameters, and current and retrospective evaluations by the participants themselves about aspects of their lives with FH since the parent studies.

5.1 Discussion of study design, subjects and methods

No one has, as far as we know, performed this type of follow-up, which include thoroughly measurements of both objective and subjective parameters.

Advantages

The genetic nature of FH necessitates lifelong lifestyle and treatment adherence, and long-term follow-up is essential. Mean follow-up from end of parent study until this current study was 10.3 years. A long-term follow-up study, such as this one, provides information about changes in the disease over time, in addition to a cross-sectional picture.

In addition to collecting biochemical parameters and other objective signs, the present study obtained the participants' subjective experiences and perceptions of having FH. Quality of life, how a chronic disease has influences on life etc. are questions few other studies have investigated.

Another advantage of this study design was the probable health benefit effects for the participants. They got to reevaluate their disease, treatment and handling of the disease after several years living with FH. They also got the possibility of having an outpatient control and obtained information from physicians.

Limitations

One limitation of this follow-up study is that we did not have a matched control group, neither of non-FH participants from the same period or of FH patients not having participated in clinical studies. Therefore, we were unable to investigate whether there was a difference compared to similar individuals with or without FH, and our results were compared with a normal population`s guidelines as well as other similar studies.

The parent studies had a total sample size of 118, and we were able to recruit 67 (56.7%). Our sample size was small, but comparable to another follow-up study of FH children and adolescents (62). FH is relatively rare (1/300-500), and among those having it there is only a portion that has been diagnosed. One assumes that one third of a total of 15-20 000 FH patients are diagnosed in Norway.

Missing data

There were variable amounts of missing data in the different analyses. In SmartDiet scores, and the biochemical and subjective parameters, there were no or only a few missing data. Naturally, for those interviewed per telephone, the clinical findings "measured BMI" and "BP" were missing. Information about "lipid deposits" was in some cases collected from the medical charts. Although the missing data may have influenced the results to some degree, the clinical findings were usually in the normal range and corresponded to the values in the general population.

Selection bias

There is a risk of non-response bias, where those individuals who refused to participate in the follow-up were systematically different from those who accepted. "The healthy volunteer effect" is a well-known phenomenon, when healthy individuals are more likely to participate in a study (63). Among the 118 participants in the previous parent studies, 67 participants were included in our follow-up, a response rate of 56.8%. There were different causes why the remaining 51 participants did not participate. Among the requested previous participants in 2013, 17 were not willing to participate for various reasons, while 10 participants were not reached. Data regarding previous participants who not participated in 2011 were missing. Probably there is some degree of selection bias, where those not participating in our follow-up had higher cholesterol levels, poorer adherence to medical treatment and diet recommendations, less frequent follow-up consultations etc.

Information Bias

Information bias may have occurred due to subjective answers in the interview and/or food questionnaire.

Reporting bias is a potential bias in the current follow-up. Under- or over reporting, e.g. when completing the SmartDiet questionnaire and responses in the interview to somewhat sensitive

questions, can not be excluded (63). Undesirable behaviors with respect to FH may have been underreported, for instance intake of saturated fat, alcohol consumption and smoking. Over reporting is most likely to have occurred regarding to e.g. physical activity, intake of fish and use of dietary supplements, which are examples of factors that contribute to good health. Two reviews concluded with a general over reporting of height and underreporting of weight, and thereby a lower self-reported BMI (64, 65). We did not make any further controls of the provided information, neither in the SmartDiet questionnaire nor in the interview, and can therefore not exclude reporting bias.

Observer- or interviewer bias occurs when the interviewers introduce errors in the questionnaire or help the participants, intentionally or not, responding in either directions (63). Interviewer's prior insight of the responders may influence the structure and the manner of presentation of the questions, which further may influence the responses (66). To avoid this bias we used similar and standardized questions for all study participants, both in 2011 and 2013. In addition, we strived to make the interviews neutral and objective. This was obtained when the same person made similar interviews in the same setting, except for the interviews made by telephone.

5.2 Discussion of statistics

Histograms and *QQ-plots* were used to evaluate normal distribution for all the parameters.

For overviewing characteristics we used *Descriptive statistics* and *Frequencies statistics*. Mainly, the results were presented with median and range (min-max) or number of subjects (n) and percent (%). We used minimum and maximum levels instead of quartiles because it illustrates the whole spectrum of the participant's values. In cases with normally distributed variables, mean ± SD were used. Most variables were not normally distributed and we therefore used median and range, as this presentation is more appropriate when the data is skewed (60). In most studies mean and SD are used for presentation of the middle value. Therefore, our median values are not completely comparable to mean values presented in other studies.

We consulted a statistician about whether parametric or non-parametric tests were most reasonable to use in our analysis. Despite a relatively large sample size (n = 67) and the fact

that e.g. cholesterol levels usually are normally distributed in the general population, many of our analysis did not meet the assumptions for normal distribution. A possible explanation may be extreme values in patients who are handling the disease improperly. We did not exclude extreme values in our study when they are both clinical important and may be numerous in some subgroups.

For data not normally distributed we used the non-parametric technique *Mann Whitney U test* to compare different parameters between groups or subgroups (60). This technique takes outliers in small sample size into consideration and uses a median as a middle value. This was advantageous in many of our analysis. To compare variables from time of diagnosis to time of follow-up we used *Wilcoxon Signed Rank Test*. Non-parametric tests may to a lesser extent discover the differences, which further may lead to loss of significant results. However, there was only one analysis, the difference in LDL-C levels in outpatient frequency the last 10 years, which was significant when we used a parametric test (*Independent Samples T-Test*, P = 0.045*)* and not significant when we used a non-parametric test (*Mann Whitney U Test*, P = 0.069*)*. Despite the fact that this result did not become statistically significant, one may assume clinical relevance. We could also have transformed the non-parametric data to meet the assumptions of the parametric tests. However, in the literature there is a considerable disagreement about usage of these techniques (60).

Parametric tests were made to verify data which showed a tendency toward a normal distribution. One should use parametric tests instead of non-parametric where it is appropriate. This is due to the differences in construction of the tests, and the fact that some statistically significant results may disappear when using non-parametric tests on normal distributed variables. We used the parametric techniques *Independent Samples T-Test* and *Paired Samples T-test* to investigate possible loss of statistically significant results when using non-parametric tests. However, these results are not included in our study.

When we stratified the study population in gender or other subgroups, there were at some occasions few subjects in each group. For instance, when comparing adherence of treatment between genders, the group which reported to forget the medication once a week or more often consisted of only 7 females and 10 males. Probable significant results may have disappeared due to the low sample size. However, the significant values obtained from the

small number of subjects in some of our analysis may indicate a strong association between the variables.

Bonferroni correction was not made in our analysis. Some significant associations may have occurred "by chance" due to multiple comparisons when we performed multiple tests on the same data material. This study is exploratory of nature and does not make any hard endpoints, and after we conferred with a statistician we decided not to use this correction or any other adjustments.

5.3 Discussion of the results

Subsequently, the principal results will be discussed and put into context of the findings in other scientific studies.

5.3.1 Study population

Our study sample included 67 relatively young participants, with an average age of 25. The distribution of gender was not statistically even, with a somewhat higher proportion of males (56.7%).

5.3.2 Previous study participation

The mean age of study start was approximately 14 years. For those who participated in more than one study the age of the last study participation were used. This may have influenced the mean age. Parents' decision was the main reason for children participating in the parent clinical trials. As the mean age of parent study start was approximately 14 years, it was expected that parents' involvement would be of great importance. Children may not be able to cope with the disease themselves, and therefore parents` involvement may be necessary to ensure proper handling. FH is a genetic disorder and at least one of the parents and often also other family members have the disease. Hence, parents typically possess some knowledge about FH in advance, and may be a good resource.

Subjective evaluation about disease and study participation

Few previous studies have investigated children`s experiences of being involved in clinical trials. According to our findings most children had positive experiences of being included in the parent clinical trials (90%), and reported to obtain benefits (70%). The positive responses

were mainly due to more frequent outpatient controls, including more knowledge about the disease. Approximately a quarter of the study population mentioned dietary advices as one of the positive experiences. The positive experiences were to some extent correspondingly to the reasons for participating, where frequent outpatient controls, better treatment and help with science were most common reasons.

A small number of studies have investigated FH-patients` own perceptions and experiences of having the disease. One study explored FH specific concerns in children and their parents regarding children`s knowledge and experiences of the disease. It found no impaired quality of life in these children. However, the results showed poor knowledge about the disease, e.g. one-third of the study population thought that FH could be cured (67).

A second study assessed the experiences of guilt and shame in FH patients. They found that the study population did not have any guilt about having the disease, but did feel guilt and shame in how they managed it (68).

Less than half of the study population reported to be concerned about having a CHD event. This finding may reflect lack of experience of disease and/or knowledge, when the risk of CHD is significant higher. On the other hand they may have knowledge about the risk, but do not let the fear influence their lives. A previous study explored FH patients' vulnerability to CVD. This study concluded additionally that FH patients develop a dynamic and personal sense of vulnerability to CVD. They describe situational factors, such as CVD in family members or experience of CHD-related symptoms, as an initiator to the dynamic perceived vulnerability (69).

Four out of five participants believed that their treatment will prevent them from having a CHD event. FH patients with proper treatment and handling, and lipid values within the reference range, have no increased risk of CHD compared to the normal population. However, an interestingly aspect is the great trust of treatment preventing them from CHD events and, at the same time, the poor adherence to treatment.

5.3.3 Outpatient control routines

Most patients continued to be monitored at the Lipid Clinic after participation in the parent studies. It is favorable for monitoring of treatment and measurements that the same clinic

performs all the outpatient controls. It is also easier to detect improvements or stagnations of the disease.

Our results illustrated the importance of frequent follow-up. Those who had their last outpatient control within two years had significant lower LDL-C levels compared to those with more than two years since last outpatient control. Although, there may be a selection bias that patients who had their last outpatient control within two years are more concerned about their disease, which may have contributed to the lower LDL-C level. The difference in LDL-C levels between the participants who were followed up every two years or more often versus the participants followed up less frequently than every two years was not statistically significant (P = 0.069). However, a larger sample size would most likely have led to a significant difference, and one may assume that more frequent outpatient controls are associated with lower LDL-C levels. Nevertheless, it may be of clinical importance.

5.3.4 Biochemical parameters

Almost half of the study population was satisfied with their cholesterol levels, while there was only 9% who achieved a treatment goal of LDL-C $\leq$2.5mmol/L. In other words, it is a discrepancy in what some participants consider as satisfactory cholesterol levels and the treatment goals. Whether the discrepancy is due to lack of knowledge about the treatment goals, or the experience that the treatment goals are too hard to achieve, is unknown. A large Dutch cross-sectional study investigated why FH patients with a LDL-C level of $\geq$2.5 mmol/L did not use maximum therapy. They found that the physicians` acceptance of a higher target LDL-C level was the main reason (70).

TC and LDL-C

Due to the large differences in lipid parameters between statin users and non-statin users, we chose to stratify data to obtain a more adequate presentation of the study population.

There was a significant (P <0.001) decrease in the TC levels of 40% in statin users from time of diagnosis to time of follow-up, but no significant (P = 0.10) decrease were found in non-statin users. This implicates that early diagnosis and subsequently adequate treatment are important for satisfactory TC levels.

According to the European guidelines on CVD prevention in clinical practice, the recommendations for subjects at high risk for CHD, including FH subjects, is TC <4.5 mmol/L (71). Although there was a significant improvement in the TC levels, the statin users had a median TC level of 5.1 mmol/L, and this subgroup in total did not reach the treatment goal.

As expected, regarding LDL-C levels at time of diagnosis and at follow-up, the same pattern as for TC levels was observed. In our follow-up, there was a significant (P <0.001) reduction in median LDL-C level among statin users of 50%, but no statistically (P = 0.55) difference in non-stain users was observed. A comparable follow-up study from the United States found a total LDL-C reduction of 43% in statin users, and concluded therefore with significantly reduced risk of CVD (62).

According to ESC/EAS guidelines, the recommended treatment goal for LDL-C is 2.5 mmol/L (21). In our follow-up, the statin users had a median LDL-C level of 3.3 mmol/L at follow-up, and only 6 (12.8%) had LDL-C levels according to the treatment goal. Among non-statin users there were none who achieved a LDL-C level $\leq$3.5 mmol/L. Our finding of a low fraction achieving the treatment goal is consistent with results from two other studies, were only 21% and 22% achieved the treatment goal. These studies suggested hesitation to prescribe the most potent medication, mainly due to the acceptance of higher LDL-C levels than the recommendations, or extremely high LDL-C levels at baseline, as probable explanations (70, 72). In 2008, National Institute for Health and Clinical Excellence (NICE) introduced a new treatment goal; a LDL-C reduction of >50%. In our study, the participants who used statins at follow-up had a reduction in LDL-C levels of 50% and are therefore achieving the new NICE treatment goal. FH patients often have extremely high LDL-C levels before initiation of treatment, and a relatively large proportion who achieved the new NICE treatment goal would not achieve a LDL-C level $\leq$2.5 mmol/L. Hence, physician using the new NICE guidelines may contribute to the low proportion achieving the original treatment goal of LDL-C $\leq$2.5 mmol/L when they accept higher LDL-C levels.

Females had a numerical lower TC level than males. Despite the lack of significant result (P = 0.24), the median difference in TC level was 0.70 mmol/L, and one may assume that the difference would have been statistically significant if there was a greater number of subjects. This was even more prominent for the LDL-C levels, where the difference was 1.3 mmol/L

and the P-value was 0.064. To summarize, our follow-up showed lower levels in TC and LDL-C in females, but the results were not significant most likely due to a small sample size. Although the differences were not statistically significant, it may be of clinical importance.

Why do females have greater reduction in TC and LDL-C levels than males?
Females had a substantially greater reduction (55%) than males (23%) in LDL-C levels. At time of diagnosis they had significantly higher levels of both TC and LDL-C. This may have contributed to the greater reduction. Nevertheless, females have numerical lower TC and LDL-C levels than males at follow-up. Another possible explanation for the greater reduction from time of diagnosis to follow-up in females is that females are more concerned and worried about their own health. However, none of our results indicated a different behavior between the genders, neither in the medication adherence (P = 0.88), use of statins at follow-up (P = 1.0), outpatient control frequency past 10 years (P = 1.0), years since last outpatient control (P = 0.80), nor in the SmartDiet score (P = 0.075). On the other hand, there were three non-statistically significant values in favor of females.

However, this is an exploratory study and the gender difference in reduction of TC and LDL-C levels were not investigated in particular.

HDL-C and TG
In our follow-up we have mainly been focused on TC and LDL-C levels, when FH arises due to defects in LDL-C metabolism and LDL-C is the main target for treatment. Nevertheless, there are separate recommendations for HDL-C and TG levels. FH patients may have lower HDL-C than the normal population, TG is generally the same as for the normal population, but it may be elevated for the same reasons as for the general population (29).

In our follow-up the median HDL-C levels in statin and non-statin users were 1.4 mmol/L and 1.3 mmol/L, respectively. The median levels were 1.5 mmol/L for females and 1.2 mmol/L for males, which was within the normal range for both genders (71). Low HDL-C is associated with increased risk of CVD in population studies (73).

According to the European guidelines on CVD prevention in clinical practice, the recommended TG levels is <1.7 mmol/L (71). The median TG levels in statin and non-statin

users were 0.7 mmol/L and 0.9 mmol/L, respectively, which was within the normal range and according to these recommendations.

ApoA-1, ApoB-100 and ApoB-100/ApoA-1

Females had a higher ApoA-1 than males (P = 0.002). As expected, due to higher LDL-C levels in our study and higher normal values, ApoB-100 levels were higher for males than females (P = 0.050). The ApoB-100/ApoA-1 in females and males was 0.67 and 1.0, respectively, and the difference was statistically significant (P = 0.001). According to this prominent difference in ApoB-100/ApoA-1 ratio, one may assume a greater risk for CVD in males compared to females in our study population. The large INTERHEART study divided the participants into quintiles based on the ApoB-100/ApoA-1 ratio, and concluded with a stepwise increased risk of CVD from low to high quintiles. Odds ratio for the highest quintile compared to the lowest was 3.87 (8). Similar results were found in the Swedish AMORIS study, were they also concluded with a stepwise increased risk ratio (7).

Lp(a) values

There was a great difference in Lp(a) levels within the two groups of gender and the range was huge between low and high values (median levels of 373 mg/L in females, and 162 mg/L in males). There was no significant difference between the genders (P = 0.077).

Several studies have investigated Lp(a) levels and risk of CHD. A Danish study, which included 9330 females and males from the general population in Copenhagen, observed a stepwise increase in risk of MI with increasing levels of Lp(a), and no threshold value was discovered (74). A large meta-analysis with patient records of more than 120 000 patients concluded with a continuous, independent and modest association between Lp(a) and risk of CHD and stroke (75, 76).

Summary biochemical parameters

The main findings regarding biochemical parameters in our study were (1) that statin users had a better lipid profile in general than non-statin users, and (2) that females had greater LDL-C reduction and lower ApoB-100/ApoA-1 ratio than males. One may therefore assume that statin users have lower risk for CVD than non-statin users, and that females have lower risk for CVD compared to males, based on the biochemical parameters.

5.3.5 Clinical findings

There was almost no difference in self-reported and measured BMI (23.2 and 23.4, respectively). This indicates good self-awareness and self-control, and there is no information bias for this parameter. Self-reported weight and height are parameters one may assume have a great risk of information bias (64, 65). Hence, this finding may strengthened other subjective results in our follow-up, when it may reduce the risk of information bias in general. As for the general population there are some participants with higher or more extreme BMI values. Participants in our follow-up had a lower average BMI than adults (40 years old) in the Oslo-area, where the average BMI in females and males are 25.2 and 26.4, respectively (77). However, there were no data for BMI in the same group of age as the study population, and the results are therefore not completely comparable.

BP increases with age and as expected in a young study population, most of the participants had normal BP values (92.7%) at follow-up.

Apart from elevated cholesterol values, clinical signs of FH are relatively uncommon, especially in young age. Only 9% of our patients had lipid deposits. A careful anamnesis with family history, biochemical tests and/or genetic tests is therefore necessary for the diagnosis of FH.

5.3.6 Medical treatment

Several studies have indicated that use of statins in children is as safe and effective as in adults (48, 51, 55, 78). However, the studies are of relatively short duration compared to the life-long treatment recommended in FH, but clinical experiences with long-term treatment from young age are increasing. In Norway, statins are recommended as cholesterol-lowering therapy to children with high cholesterol levels or family history of CHD or CVD from the age of 8-10 years (47). Those are the same guidelines which are proposed in a recent review. They concluded that statin treatment can be initiated at 8 years of age, when no harmful effects are observed. However, a long-term multicenter study with a large study population is needed to reveal potential long-term side effects in children (78).

In our study, most participants on statins used Atorvastatin at follow-up, median dose 40 mg/day. The median dose Simvastatin at follow-up was also 40 mg/day. A randomized, double-blinded clinical trial performed on 325 patients with FH concluded that a high-dose

(80mg) Atorvastatin produced a larger reduction in LDL-C level (8.0 vs.3.9 mmol/L) than conventional dose (40 mg/day) Simvastatin (8.3 vs.4.8 mmol/L). High-dose Atorvastatin also produced a significant reduction in carotid intima media thickness compared to an increase with Simvastatin (79). Another study which compared high-dose Atorvastatin (80mg) versus Simvastatin (40mg/day) concluded that Atorvastatin is the most efficient statin in treatment of FH patients, and induces regression of atherosclerosis (80). Due to the more potent effect, Atorvastatin is usually preferred instead of Simvastatin at the Lipid Clinic.

19 of 67 (28.4%) participants did not use statins at follow-up. A Dutch cohort study who observed more than 2000 patients with FH, found a 76% overall risk reduction for CHD among patients with statin treatment relatively no statin treatment. Most of the participants in the cohort study (n = 1067) used Simvastatin (mean dose of 33mg), which provided a LDL-C reduction of 44%. Another 221 participants used Atorvastatin (mean dose of 49mg) which contributed to a reduction of 49% in LDL-C level. During statin treatment the mean TC, LDL-C and HDL-C levels in the cohort study were 5.9 mmol/L, 4.0 mmol/L and 1.28 mmol/L, respectively. These findings indicate the importance of long-term statin-treatment, despite of not achieving the treatment goal of LDL-C $\leq$2.5mmol/L (45). In addition, a British long-term prospective registry study with 3382 participants with FH found a coronary mortality reduction of one-third since use of statins in greater extent. It also showed a significant reduction in all-cause mortality and fatal cancer (46). This emphasizes the importance of taking the cholesterol-lowering medication when having FH.

Side effects of treatment

Side effects that occurred most frequently among the study population were abdominal complaints (46.2%) such as flatulence, constipation, nausea and diarrhea, in addition to muscle/joint pain and fatigue. These are side effects specified as usual for statins (47).

A high proportion (n = 19, 73.1%) of the participants who reported side effects discontinued or changed the medication. 7 of them stopped the medical treatment permanently, which is very unsatisfactory according to LDL-C levels, which is illustrated in the difference between current statin users and non-statin users in our follow-up.

Adherence

As much as 60% of the statin users reported that they forget to take their cholesterol-lowering medicine 1-2 times a month or more often. The poor adherence to statin therapy is startling with respect to the great risk of hazardous disease due to unsatisfactory treated FH. A review stated that adherence may be even more challenging in adolescents due to the unique development, psychosocial factors and lifestyle issues (81). A standard routine of taking the medication is beneficial, and thoroughly education about the importance of adequate and continuously treatment may be of great value. However, despite the relatively poor adherence in statin users the difference between current statin users and non-statin users is astonishing.

Potential reasons for not taking cholesterol-lowering medication

Firstly, side effects and poor routines were the main reasons for why participants did not use medication at follow-up. Although side effects may occur, they are dose-dependent and may disappear or lessen in intensity when the dose is reduced. Patients may also react differently to different statins, and switching statin can also be an option. Adequate advice and frequent monitoring is necessary to ensure good routines and prevent participants from quitting medication.

Secondly, infrequent monitoring may be a potential reason for quitting medication. In our follow-up study there was a significant difference in number of years since last outpatient control between current statin users and non-statin-users, $P = 0.021$.

Thirdly, hypercholesterolemia is often an asymptomatic disease, and patients may not experience any symptoms. More than 90% of the participants subjective considered their health as average or better than average. The lack of experiences and symptoms of the disease may further lead to the perception that they do not need their cholesterol-lowering medicine, despite the risk of hazardous outcomes. In our study there were more frequently the participants` grandparents that had suffered CVD than the parents. This may further lead to a greater distance to the disease, and the perception of not having increased risk of disease compared to the normal population.

There was only one person who stopped medication due to breast feeding. Statin therapy is contraindicated from three months before planned pregnancy, during pregnancy and when

breastfeeding (82).

5.3.7 Diet and lifestyle

Diet and SmartDiet score

All participants in the parent trials have previously received advices on cholesterol-lowering diet at the Lipid Clinic. The SmartDiet questionnaire is the scoring sheet we used to evaluate heart-friendly diet and lifestyle status. Diet in FH children and young FH subjects versus non-FH children and young subjects were investigated in a previous study. Findings in this study showed a higher SmartDiet score in FH children than in non-FH participants, and a more favorable diet regarding the public recommendations. They also found that FH children had healthier food choices than non-FH children, particularly with respect to the most important sources for saturated fat. The age group 18-28 years had a median level of 33 (33). In our follow-up, with a median SmartDiet score of 32.5, the participants had a "middle score". However, in this high-risk population further improvements may be beneficial, and the patients should still be advised and motivated to obtain a better diet and lifestyle.

A limitation of the SmartDiet score is that it does not quantify the intake of the foods. It was therefore difficult to compare the scores with the public recommendations. Nevertheless, it may be a good tool to identify diet and lifestyle status. It is filled out rapidly by the participants, and also time saving for the investigators. The difference in median LDL-C levels in participants with SmartDiet score of >27 compared to LDL-C level in participants with SmartDiet score of <27 was 1.3 mmol/L. The difference was not significant (P = 0.70). We may therefore not conclude with an association between high SmartDiet score and beneficial LDL-C levels. However, the difference may be of clinical relevance, and a small number of subjects (n = 8) in the group of low SmartDiet score may have contributed to the lack of significant results. Other possible explanations are (1) the fact that relatively small differences in diet is of limited importance compared to e.g. statin treatment, (2) that the SmartDiet scoring sheet has too low sensitivity, (3) information bias or misunderstanding of the scoring sheet, or (4) that the participants` diet and lifestyle habits are quite similar.

Smoking

In our study population there were 7.6% who smoked regularly and 7.6% were party-smokers. This was a relatively small proportion compared to the general Norwegian population, where around 15% smokes daily and 9% occasionally (83). As mentioned above, smoking is a

strong risk factor for atherosclerosis and CVD (6, 84). The Nurses` Health Study (NAHNES) found a positive association between the number of cigarettes smoked per day and risk of fatal CHD, and increasingly risk with increasingly number of cigarettes. Even 1-4 cigarettes per day were associated with a twofold increased risk of fatal CHD (85). As this group already has a high risk for CHD, the patients should be tried motivated to eliminate additional risk factors such as use of tobacco (86, 87).

Physical activity

American College of Sports Medicine and the American Heart Association (1995, updated 2007) found an inverse association between increasing physical activity and risk of CHD (88). This inverse association is also stated in a report published by Word Health Organizations

The participants in our study used in median 1.0 hour on body strength and 2.5 hours on endurance per week. The Nordic Recommendations 2012 recommends that "Adults should engage in at least 150 minutes of moderate-intensity physical activity throughout the week, or engage in at least 75 minutes of vigorous-intensity physical activity throughout the week, or engage in an equivalent combination of moderate- and vigorous-intensity activity" (89). In median, the participants in our follow-up had a higher physical activity level than suggested in the recommendations. However, the range among the participants was great, and some participants may obtain benefits of increasing their activity level.

Multiple dietary and lifestyle factors

Earlier studies have concluded that dietary and lifestyle factors together have a more powerful effect on CHD risk than any single factor alone. The great risk reduction among women in the Nurses` Health Study and Health Professionals` follow-up study was detected in those who did not smoke, were not overweight, maintained a healthful diet, exercised moderately on a daily basis, and consumed moderately amounts of alcohol (84).

6. Conclusion and clinical implications

In our follow-up study we have shown that

A. statin users had a significantly lower LDL-C level than non-statin users. Although the difference was huge, few statin users achieved the treatment goal of LDL-C $\leq$2.5 mmol/L. Despite the high risk of hazardous outcomes of severe hypercholesterolemia, 19 of 67 participants did not use statins at time of follow-up.

B. there was a greater reduction in LDL-C levels from time of diagnosis to follow-up in females than in males. None of our analysis found an explanation for the greater reduction. There was no difference in (1) medical adherence, (2) use of statins (3) frequency of outpatient controls (4) years since last outpatient control or (5) SmartDiet scores. Females had also a significantly lower ApoB-100/Apo-A1 ratio than males.

C. participants who more recently had their last outpatient control had a significantly lower LDL-C level. There was also a numerical lower LDL-C level among participants with more frequent outpatient control. However, the difference was not statistically significant most likely due to small sample size, and the result may be of clinical importance.

D. there was no significant association between SmartDiet scores and LDL-C levels.

E. most children had positive experiences of being included in the parent studies and reported to obtain benefits. An interestingly aspect was the great trust of treatment preventing them from CHD events, and at the same time, the poor adherence.

In conclusion, our findings show the importance of statin treatment to obtain a more beneficial LDL-C level. Statin users obtained a considerably reduction in LDL-C level from diagnosis to follow-up, and their levels were far lower compared to non-statin users. Adequate education about the effect of statin treatment and a thoroughly follow-up of medication history may be necessary to ensure maintenance of statin treatment, when poor routines and side effects were the main reasons for quitting medication and poor adherence. Females had a greater reduction in LDL-C levels and lower ApoB-100/ApoA-1 ratio than males, which may suggest a lower risk for CVD. Furthermore, close and frequent follow-up were associated

with reduced LDL-C levels, which implicates the importance of regularly contact between FH patients and a specialized health center.

7. Future perspectives

This follow-up has generated new knowledge particularly regarding the importance of frequent and close outpatient controls, and the participants' subjective experiences of having FH and being included in a study. These are aspects of FH and other chronic diseases where limited research exists.

The present study has shown that a huge proportion of the participants stopped taking their cholesterol-lowering medication/statins based on their own decision, and for further treatment and monitoring of FH patients at the Lipid Clinic this area will be very important to intercept and prevent.

Moreover, there are generated a basis for further research and hypotheses, among other why females have greater reduction in LDL-C levels than males. In this exploratory study we did not investigate this gender difference in particular, and welcome future studies to do so.

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List of appendices

Appendix 1: Approval from the Regional Committee of Medical Ethics

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Øyvind Straume	55978497	01.07.2013	2013/985/REK vest
			Deres dato:	Deres referanse:
			28.05.2013	

Vår referanse må oppgis ved alle henvendelser

Gisle Langslet
Forskningsveien 2B, Postboks 4950 Nydalen

2013/985 Langtidsoppfølgning av barn med Familiær Hyperkolesterolemi etter deltakelse i kliniske studier

Forskningsansvarlig: Oslo Universitetssykehus HF
Prosjektleder: Gisle Langslet

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 20.06.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Familiær hyperkolesterolemi (FH) er en autosomal dominant, arvelig sykdom med redusert antall LDL-reseptorer, redusert opptak av LDL-kolesterol fra blod til lever, høyt blodkolesterol, økt kolesterolavleiring i blodåreveggene og økt risiko for koronar hjertesykdom i voksen alder. I 2011 ble det gjort en etterundersøkelse av FH-barn som hadde deltatt i to studier ved Lipidklinikken i 2000-2001. 32 deltakere ble etterundersøkt. Resultatene indikerte faktorer med prognostisk betydning. Forskergruppen ønsker nå spørre 7 deltakere som ikke svarte i 2011 og ytterligere 78 deltakere i 4 andre studier ved Lipidklinikken i perioden 1999-2008 om tilsvarende etterundersøkelse, og slå dette sammen til et større materiale for å styrke funnene.

Vurdering

Søknad/protokoll
Komiteen anser dette som et forsvarlig opplegg, som det er ufarlig å delta i.

Samtykke
Prosjektleder legger opp til å innhente samtykke for alle data, men vil også hente inn data fra pasientjournal fra de som ikke svarer på henvendelsene som en "kvalitetssikring." Samtykke er den klare hovedregelen i alle medisinske forskningsprosjekter, og det er ikke mulig å plukke ut enkelte biter av prosjektet og kalle det kvalitetssikring for å slippe å innhente samtykke. Komiteen setter som vilkår at samtykke innhentes for alle data, og at ikke-respondenter ikke inkluderes i studien.

Purring
Prosjektleder ønsker å gjennomføre purring per telefon, men komiteen aksepterer ikke dette i denne saken. Komiteen aksepterer en purring, men kun at dette gjøres per brev.

Prosjektslutt og lagring av data
Tillatelsen til å behandle data i prosjektet gjelder til prosjektslutt 31.12.2014. Søker ønsker å oppbevare

Besøksadresse:
Haukeland Universitetssykehus, Sentralblokken, 2. etg, Rom 4617

Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK vest og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK vest, not to individual staff

studiepermer i 15 år etter prosjektslutt. REK Vest godkjenner ikke dette, men tillater opp til fem års oppbevaring av avidentifiserte studiedata for etterkontroll. Data skal deretter slettes eller anonymiseres.

Dersom det senere viser seg å være behov for ytterligere oppbevaring av data, må det søkes REK Vest om forlengelse via søknad om prosjektendring før tillatelsen løper ut.

Vilkår

- Samtykke skal innhentes for all datainnsamling, og ikke-respondenter skal ikke inkluderes.
- Data kan kun oppbevares avidentifisert opp til fem år etter prosjektslutt for etterkontroll.
- Purring skal kun gjøres per brev.

Vedtak
REK Vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2015, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

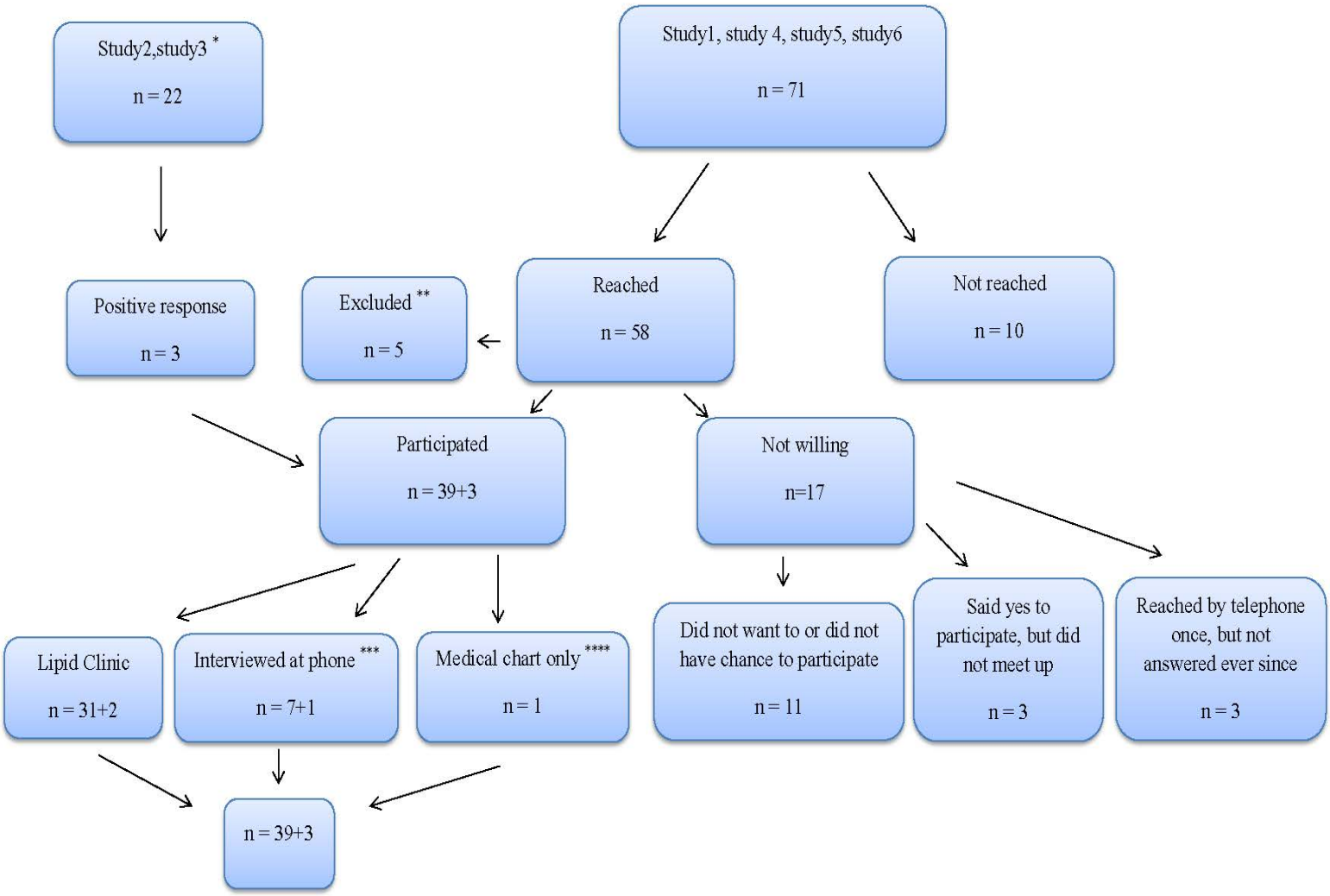
Med vennlig hilsen

Jon Lekven
komitéleder

Øyvind Straume
seniorkonsulent

Kopi til: oushfdlgodkjenning@ous-hf.no

Appendix 2: Flowchart of participants interviewed by the master student



* Not reached or not willing to participate in 2011
** Previous participated in study1, but did not have FH after all
*** Did not meet up for outpatient control at the Lipid Clinic
**** Consented us to use information from medical chart

Appendix 3: Request for participation in the follow-up project

”Langtidsoppfølgning av barn med Familiær Hyperkolesterolemi etter deltakelse i kliniske studier”

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å se hvordan det har gått med barn som har deltatt i utprøvinger av kolesterolsenkende medisiner og plantesteroler i Norge.

Hva innebærer studien?

Studien innebærer et telefonintervju eller at du møter opp ved Lipidklinikken personlig. Det vil bli spurt om ”vanlige journalopplysninger” som blant annet vekt, høyde, blodtrykk, lipidverdier, allergier, kosthold, tidligere sykdommer, medikamentbruk og eventuelle bivirkninger av medikamentene. Du vil også bli spurt om hvordan det er å leve med familiær hyperkolesterolemi (FH) og hvordan du vurderer behandlingen og oppfølgingen du har fått. Deltakere som ønsker utvidet vurdering vil få tilbud om poliklinisk time/vurdering ved Lipidklinikken. Dersom det er mer enn 6 måneder siden du sist målte kolesterolnivået, dersom du har endret behandlingsopplegg siden forrige blodprøve, eller dersom tidligere prøver ikke inneholder alle blodprøvesvarene vi ser etter, vil du bli spurt om å avgi en blodprøve for å måle dette, i tillegg til vanlige sikkerhetsblodprøver.

Mulige fordeler og ulemper

Ulempe for deltakerne vil være tidsforbruk. Mulige fordeler vil være gjennomgang av sykehistorie og eget behandlingsopplegg.

Hva skjer med prøvene og informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, må du undertegne samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte overlege Gisle Langslet på telefon 23 075 603 eller mobil 90 144 284.

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

Kriterier for deltakelse

Voksne (>18 år) som tidligere har deltatt i kliniske studier ved Lipidklinikken mens de var barn (<18 år) vil få forespørsel om deltakelse per brev og/eller telefon. Totalt er dette 85 personer.

Bakgrunnsinformasjon om studien

Familiær hyperkolesterolemi (FH) er en arvelig, autosomal dominant sykdom hvor genfeil fører til redusert antall LDL-reseptorer. Dette fører til høyt kolesterol fra de første leveår og åreforkalkninger allerede fra puberteten. Tidlig og livslang kolesterolsenkende behandling, hovedsakelig med statiner, forhindrer åreforkalkninger og gir omtrent like god livsprognose som normalbefolkningen. Lipidklinikken utførte i 1999-2000 en studie med bruk av plantesterolmargarin til barn med FH og deltok i flere studier med kolesterolsenkende medisiner i perioden 1999-2008. I 2011 ble det gjennomført en intervju-undersøkelse av 32 deltakerne i to av disse studiene. Vi ønsker nå å etterundersøke deltakerne som ikke ble undersøkt i 2011 og slå dette sammen til ett forskningsmateriale.

Undersøkelser, blodprøver og annet den inkluderte må gjennom

Se beskrivelse på side 1 under avsnittet: *Hva innebærer studien.*

Tidsskjema – hva skjer og når skjer det?

Intervjuene vil bli gjennomført i løpet av 2013 og 2014.

Kapittel B - Personvern, økonomi og forsikring

Personvern

Opplysninger som registreres om deg er ”vanlige journalopplysninger” som blant annet alder, kjønn, vekt, høyde, blodtrykk, lipidverdier, allergier, kosthold, tidligere sykdommer og medikamentbruk og eventuelle bivirkninger av medikamentene. Oslo Universitetssykehus Rikshospitalet ved administrerende direktør er databehandlingsansvarlig.

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 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.

Økonomi

Prosjektet gjennomføres av Lipidklinikken og det er ingen økonomiske interesser i prosjektet.

Forsikring

Da dette er en intervju-undersøkelse er det ingen forsikring av studiedeltakere. Eventuell blodprøvetaking vil være ledd i vanlig poliklinisk oppfølging. Blodprøvetaking er forbundet med svært liten risiko, men eventuelle skader vil måtte meldes til Norsk Pasientskadeerstatning og dekkes på vanlig måte for poliklinisk virksomhet.

Informasjon om utfallet av studien

Resultatene fra studien vil bli sammenskrevet og forsøkt publisert i et vitenskaplig tidsskrift. Et populærvitenskaplig sammendrag vil bli tilsendt deltakere etter publisering.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

(Navn med blokkbokstaver)

Stedfortredende samtykke når berettiget, enten i tillegg til personen selv eller istedenfor

---

(Signert av nærstående, dato)

(Navn med blokkbokstaver)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

(Navn med blokkbokstaver)

De gode rådene finner du her

Mettet fett er kolesteroløkende. Reduser derfor inntaket av matvarer med mye mettet fett. Velg i stedet matvarer med umettet fett som kan senke kolesterolet.

Drikk mager melk, ½ liter skummet, sot eller sur, daglig. Dersom du ikke drikker melk daglig, kan det føre til et for lavt inntak av kalsium.

Alle fløte- og rømmetyper inneholder mye mettet fett og anbefales ikke i hverdagskostholdet. Cultura, skummet kultur, lettmelk, ekstra lett melk, skummet melk, yoghurt, mager Créme Fraiche (10 % fett) og Kesam (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 brødskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen. Velg gjerne planteoljebaserte oster som pålegg og i matlagingen.

Fett kjøtt er også en kilde til store mengder mettet fett. Velg kjøtt med mindre enn 10 % fett både som middagsmat og som pålegg. Skjær bort alt synlig fett, og spis minst mulig oppblandede kjøttprodukter. Velg for eksempel karbonadedeig eller kylling-/ svinekjøttdeig fremfor kjøttdeig. Fjern skinnet på kylling, kalkun og annet fjærkre. Velg skinkeprodukter som pålegg fremfor salami, fårepølse og lignende.

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

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

Bruk gjerne olje, flytende eller myk plantemargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg heller kokt eller ovnsstekt mat, da vil behovet for fett i matlagingen reduseres.

Grove kornprodukter er viktig i hverdagskostholdet. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brødet bør inneholde mer enn 6 gram fiber pr 100 gram brød. Se også etter Brødskala'n på emballasjen.

Husk "5-om-dagen". Spis minst tre porsjoner grønnsaker og to porsjoner frukt hver dag. Fyll halve middagstallerkenen med grønnsaker, både rå og lettkokte. Spis frukt og grønnsaker som mellommåltid, som pålegg og som pynt på pålegget. Vær raus med porsjonene. Erter, bønner og linser kan med fordel spises ofte.

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

Bruk minst mulig sukker, sukkerholdig mat og drikke, som kjeks, kaker, is, søtt pålegg, sukkergodt, 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 fruktsukker) kan også øke triglyseridverdiene.

Nøtter og mandler inneholder gunstig umettet fett, men er veldig kaloririke. Bruk det derfor gjerne, men i begrenset mengde. Kokosnøtten og chillinøttene inneholder mye mettet fett og bør derfor unngås.

Kaffebønnen inneholder fettstoffer som øker kolesterolet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert, da filteret fjerner det meste av fettstoffene. Husk at kaffe tilsatt melk (for eksempel café latte, cappuccino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffe som drikkes.

Alkohol inneholder mye kalorier og kan derfor føre til vektøkning. Alkohol kan også øke triglyseridverdiene.

Eggeplommen inneholder mye kolesterol. Begrens inntaket til to eggeplommer per uke. Den største årsaken til økning av kolesterolet i blodet er likevel matvarer rike på mettet fett.

Spørreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer informasjon om kostholdet i heftet "Kostbehandling ved høye blodlipider hos voksne" (Lipidklinikken 2006).

Spørsmål 1-15 med unntak av spørsmål 10 er evaluert i forhold til veid kostholdsregistrering.

Kilde: Svilaas A, Strøm EC, Svilaas T, Borgejordet Å, Thoresen M, Ose L. SmartDietTM, a health educational tool. Reproducibility and validity of a short food questionnaire for assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60-70. Tredje revidering av skjemaet utgitt i mai 2009.

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Les spørsmålene og de angitte svarmulighetene 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 en del punkter, slik at det blir mer helse- og hjertevennlig.
36 poeng eller mer:	Du har sunne kostholdsvaner.

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

Sett ett kryss til hvert spørsmål ved å krysse av i sirkelen ved det alternativet som passer best med det du vanligvis spiser.
Vær oppmerksom på at spørsmålene veksler mellom å spørre etter daglig og ukentlig forbruk.

1. Melk (sur/søt) og yoghurt

Hvor mange glass melk drikker/bruker du daglig som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te o.l.? Antall:.....

Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke? Antall:.....

Hvilken type melk bruker du oftest?

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett .....
Lettmelk • Cultura • Biola naturell (syrnet lettmelk) • Ekstra Lett melk • Melk med smak .....
Skummet melk • Skummet kultur melk • Biola bærdrikk 0,1 % fett .....
Drikker/bruker mindre enn 1 liter melk i uken eller bruker aldri .....

2. Fløte, rømme o.l.

Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te o.l.

Kremfløte • Crème Fraiche • Seterrømme • Pisket krem .....
Matfløte • Lettrømme • Crème Fraiche lett .....
Kaffefløte • Ekstra lett rømme • Vikingmelk • Kesam • Matyoghurt • Crème Fraiche 10 % fett..
Bruker ikke dette ukentlig eller bruker aldri .....

3. Ost på brødmaten, i matlaging, på pizza o.l.

Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost), spiser du daglig? Antall:.....

Til hvor mange middager per uke bruker du ost? (eks pizza, lasagne, i saus, i salat o.l.) Antall:.....

Hvilken type ost bruker du oftest?

Hvitost • Nokkelost • Gudbrandsdalsost (G35) • Ekte geitost • Flotemysost • Edamer •
Gråddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Revet pizza-/pastaost •
Taffelost • Burgerost • Snøfrisk • Parmesan .....
Lettere hvitost • Lettere nøkkelost • Lettere flotemysost • Lettere Gudbrandsdalsost •
Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak .....
Ost med rape- og solsikkeolje (Vita Gul o.l.) • Cottage cheese • Gammelost • Pultost •
Mager mysost • Prim • Mager prim • "Så lett" ost 10 % fett .....
Bruker ost kun en gang i uken eller bruker aldri. .....

4. Kjøttpålegg

Hvilken type kjøttpålegg bruker du oftest?

Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse •
Reinsdyrpølse • Falukorv • Reskepølse • Sylte • Lammerull • Paté • Fenalår •
Leverpostei (vanlig). .....
Kokt/rokt skinke • Hamburgerrygg • Krydderskinke • Pastramiskinke • Roastbiff • Bankekjøtt •
Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand •
Oljebaserte posteier (Vita, Mills, Delikat, Gilde) • Mager leverpostei. .....
Bruker kjøttpålegg kun en gang i uken eller bruker aldri .....

5. Kjøtt til middag

Hvilken type kjøtt bruker du oftest?

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse •
Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake •
Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt .....
Kjøttdeig (okse, lam) • Kyllingpølse • Lettpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt •
Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand •
Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand •
Hamburgerrygg med fettrand .....
Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt •
Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett •
Kylling, kalkun og høne uten skinn • "Go og mager" polser • Vita polser. .....
Spiser kjøtt kun en gang i uken eller spiser aldri .....

6. Fiskepålegg

Hvor ofte har du fisk som pålegg eller i salater til lunsj?

Eksempel: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker o.l.

På inntil 1 brødskive i uken eller aldri .....
På 2-4 brødskiver i uken. .....
På 5 eller flere brødskiver per uke .....

7. Fisk til middag

Hvor mange ganger i uken spiser du fisk, fiskemat og/eller fiskeretter?

Inntil en gang i uken eller aldri .....
2 ganger i uken .....
3 eller flere ganger i uken .....

Til hvor mange av disse middagene spiser du fet fisk ukentlig? Antall:.....

Eksempel: Ørret • Laks • Makrell • Kveite • Sild

8. Majones, remulade og kaviar

Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?

Eksempel: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix o.l.

På inntil 1 brødskive i uken eller aldri .....
På 2-7 brødskiver i uken. .....
På 8 eller flere brødskiver per uke. .....

9. Smør eller margarin på brødmaten

Hvilken type bruker du oftest?

Meierismør og alle andre typer smør • Smøregod • Bremyk • Brelett • Brelett Oliven •
Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta .....
Soft Flora (beger) • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin •
Olivero • Solsikke margarin • Soft Ekstra • Brelett omega-3 margarin .....
Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin. .....
Bruker vanligvis ikke smør eller margarin på brødmaten. .....

10. Plantesteroler

Bruker du et produkt som inneholder plantesteroler?

Eksempel: Vita Pro-aktiv • Becel Pro-aktiv ◯ Ja ◯ Nei

11. Fett i matlagingen

Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing o.l.

Meierismør og alle andre typer smør • Bremyk • Smøregod • Melange margarin (kube) •
Per margarin • Soft Flora stekemargarin (kube) • Soya stekemargarin • Palmeolje. .....
Soft Flora (beger) • Soya margarin • Solsikke margarin • Oliven margarin • Olivero •
Soft Ekstra. .....
Olje • Flytende margarin • Vita .....
Bruker vanligvis ikke fett i matlagingen .....

12. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig? Antall:.....

Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokostblandinger spiser du ukentlig? Antall:.....

Hvilken type brød og kornprodukter spiser du oftest?

Kneippbrød • Firkornbrød • Landbrød • Jegerbrød • Loff • Fine rundstykker • Baguetter •
Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter •
Frokostkorn (med sjokolade, honning, sukker) o.l. .....
Rugbrød • Pumpernikkel • Bakers havre-, spelt- og byggbrød • Vita brød •
Gorman havrebrød • Mesterbakeren grovbrød • Birkebeinerbrød • Mørke knekkebrød •
Rugspro • Fiberrik • Havregryn • Weetabix • Havrefras • Shredded wheat o.l. .....
Spiser ikke brød, knekkebrød eller andre kornprodukter .....

13. Grønnsaker, frukt og bær

Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?

1 porsjon = 150 g som tilsvarer ca 2 gulrøtter eller ca et stort eple

Mindre enn 2 porsjoner (< 300 g). .....
2-4 porsjoner (300-600 g). .....
Mer enn 4 porsjoner (> 600 g) .....

Hvor mange av disse porsjonene er grønnsaker? Antall:.....

Hvor mange ganger i uken spiser du salat til lunsj? Antall:.....

14. Søt pålegg og søt drikke

Hvor ofte bruker du søt pålegg eller søt drikke med sukker eller fruktsukker?

Eksempel: Syltetøy • Marmelade • Prim • Geitost • Sjokoladepålegg • Honning • Brus • Saft • Fruktjuice/juice • Nektar o.l.

0-1 ganger daglig. .....
2 ganger daglig. .....
3 eller flere ganger daglig. .....

15. Sjokolade, snacks, kaker, kjeks o.l.

Hvor ofte spiser du snacks?

Eksempel: Sjokolade • Fløteis • Potetgull • Ostepop • Baconcrisp • Tortilla chips • Kaker • Kjeks • Smågodt o.l.

0-1 ganger ukentlig .....
2 ganger ukentlig .....
3 eller flere ganger ukentlig .....

Totalt antall poeng: =

16. Belgvekster

Spiser du belgvekster ukentlig? ◯ Ja ◯ Nei

Eksempel: Hvite tomatbønner • Brune bønner • Kikerter • Linser • Erter • Sukkererter o.l.

17. Potet, ris og pasta

Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?

En porsjon tilsvarer 2 poteter eller 2 dl kokt ris eller 2 dl kokt pasta/spaghetti

◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

Hva spiser du oftest? ◯ Potet ◯ Ris ◯ Pasta

18. Nøtter, mandler o.l.

Spiser du nøtter/mandler ukentlig? ◯ Ja ◯ Nei

Spiser du avokado eller oliven ukentlig? ◯ Ja ◯ Nei

19. Kaffe

Drikker du kaffe? ◯ Ja ◯ Nei

Hvis ja, hvilken type? .....

Eksempel: Cappuccino • Café latte • Presskannekaffe • Kokekaffe • Traktekaffe • Pulverkaffe o.l.

20. Alkohol

Drikker du alkohol? ◯ Ja ◯ Nei

Hvis ja, hvor mange enheter drikker du til sammen per uke?
◯ Mindre enn 1 ◯ 1-7
◯ 8-14 ◯ 15 enheter eller flere

1 enhet =
1 glass vin (125 ml)
1 glass øl (0.33 l)
4 cl brennevin

21. Egg

Hvor mange egg, inkludert i matlaging, spiser du per uke? Antall.....

1. Måltidsmønster

Hvor mange måltider, inkludert mellommåltider, spiser du daglig?
◯ 1-2 måltider ◯ 3 måltider
◯ 4 måltider ◯ 5 eller flere måltider

2. Høyde, vekt og midjemål

Høyde: ..... cm Vekt: ..... kg

Ønsker du å gå ned i vekt? ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

Midjemål: ..... cm (Fylles ut av helsearbeider)

3. Røyk/snus

Røyker du? ◯ Nei ◯ Ja ◯ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du i gjennomsnitt per dag? Antall .....

Snuser du? ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du i gjennomsnitt per dag? Antall .....

4. Mosjon

Hvor ofte mosjonerer du i minst 30 minutter slik at du blir lett andpusten eller svett?

Eksempel: Rask gange • Løping • Skigåing • Svømming • Sykling o.l.

◯ Sjeldnere enn 1 gang per uke eller aldri
◯ 1 til 2 ganger per uke
◯ 3 eller flere ganger per uke

Hvilken type mosjon bedriver du? .....

5. Kosttilskudd

Bruker du kosttilskudd?
◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler
◯ Multivitaminpreparat ◯ Annet .....

Appendix 5: «Reminder-letter»

Kjære FH-pasient,

Vi skriver til deg fordi du har deltatt i en studie for barn og unge med utprøving av kolesterolsenkende medisin på Lipidklinikken, og fordi du tidligere har fått en forespørsel om å delta i en oppfølgingsstudie etter dette.

Vi har ikke greid å komme i kontakt med deg etter den første forespørselen og vil derfor spørre deg pånytt om du vil delta i en slik oppfølging, se vedlagte pasientinformasjon.

Som ledd i oppfølgingsstudien vil du også kunne få tilbud om en time til legekontroll på Lipidklinikken. Vi har erfaring for at jevnlig oppfølging er av stor betydning for behandlingen ved familiær hyperkolesterolemi.

TA KONTAKT
Hvis du er interessert i å delta ber vi deg ta kontakt med oss.

Kontaktpersoner:

Gisle Langslet, lege, Tlf. 23 075 617
Ida Halvorsen, masterstudent, Tlf. 924 55 393

Dersom du ikke ønsker å delta i oppfølgingsstudien, ber vi om ditt samtykke til å innhente opplysninger fra din fastlege eller behandlende lege om hvilket kolesterolnivå du har og hvilken behandling du får for høyt kolesterol. Dette er også viktig informasjon for oss, da vi gjerne vil vite hvordan utviklingen har vært hos unge FH pasienter. Du må da skrive under på samtykket nedenfor, og returnere det i vedlagte returkonvolutt.

SAMTYKKE

Jeg samtykker til at Lipidklinikken kan innhente opplysninger fra min fastlege eller behandlende lege om hvilken behandling jeg får for familiær hyperkolesterolemi og resultater av blodprøver i forbindelse med behandlingen.

Signatur: Dato:

Navn med blokkbokstaver:

Appendix 6: Questions used in the interview (in Norwegian)

Hvem bestemte at du skulle delta i studien?
Hva var grunnen til at du/foreldrene dine ønsket å delta i studien?
Hvor enig eller uenig er du i påstanden "som barn opplevde jeg det som veldig slitsomt å delta i studien"
Helt enig, Delvis enig, Verken uenig eller enig, Delvis uenig, Helt Uenig
Hvor enig eller uenig er du i påstanden "nå i ettertid ser jeg på det å ha vært med på studien som noe positivt"
Fikk du noe spesielt ut av studien enten positivt eller negativt som du vil kommentere?
Fullførte du studien?
Hvis ikke fullført, hvorfor stoppet du før tiden?
Hvis fullført, opplevde du noen bivirkninger i løpet av studien?
Hvor mange år etter studien gikk det før du fikk oppfølgning?
Hvor mange år etter studien gikk det før du fikk oppfølgning?
Hvor var det første stedet du fikk oppfølgning etter studien?
Har du byttet oppfølgning senere?
Hvis ja, hvorfor byttet du?
Hvor mange ganger i året har du vært til oppfølgning av ditt høye kolesterol i de siste ca 10 årene?
Husker du omtrent hva totalkolesterol har vært (i "snitt") disse 10 årene?
Husker du omtrent hva LDL har vært (i "snitt") disse 10 årene?
Husker du omtrent hva HDL har vært (i "snitt") disse 10 årene?
Husker du omtrent hva triglyserider har vært (i "snitt") disse 10 årene?
Hvordan tror du kolesterolet har endret seg siden studien?
Hvilke medisiner har du gått på siden studien?
Hvis du ikke fikk kolesterolsenkendemedisin rett etter studien - vet du hvorfor det tok lang tid?
Bruker du kolesterolsenkende medikamenter på resept idag?
Hvis ja, type og dosering
Bruker du naturmedisiner for kolesterolet?
Når ble kolesterolverdiene dine målt sist?
Hva er de nyeste kolesterolverdiene dine? (totalkolesterol)?
Hva er de nyeste kolesterolverdiene dine (HDL)?
Hva er de nyeste kolesterolverdiene dine? (LDL)?
Hva er de nyeste kolesterolverdiene dine? (triglyserider)?
Hva er de nyeste kolesterolverdiene dine (ApoA1)?
Hva er de nyeste kolesterolverdiene dine (ApoB)?
Hva er de nyeste kolesterolverdiene dine? Lp(a)?
Hva er de nyeste kolesterolverdiene dine? ASAT?
Hva er de nyeste kolesterolverdiene dine? ALAT?
Med tanke på dette blodrpøvesvaret hvor enig eller uenig er du i påstanden: "jeg er fornøyd med kolesterolverdiene mine"?
Helt enig, Delvis enig, Verken uenig eller enig, Delvis uenig, Helt Uenig
Hvis uenig hva er grunnen til åt du ikke bruker større dose eller flere medikamenter?
Siden studien, har du opplevd bivirkninger av kolesterolsenkende medisiner?
Hvis ja, av hvilke medisiner?
Hvis ja, hvilken type bivirkning?
Hvis du noen gang har hatt bivirkninger, hvordan har det påvirket din livskvalitet?
Hvis ja, hvordan har det påvirket behandlingen din?
Hvis ja, hvem har diagnostisert bivirkningene?
Hvis ja, har det vært utslag på blodprøver?
Hvis ja, hvor enig/uenig er du i påstanden, "jeg er helt sikker på at bivirkningene har skyldtes medisinen og ikke vært vanlige kroppslige plager som kommer fra tid til annen"
Helt enig, delvis enig, verken enig eller uenig, delvis uenig, helt uenig
Hvis ja, har bivirkningene ført til at du har sluttet med medisinen over en lengere periode (over 14 dager)?
Hvis ja, hvor lenge?
Fører bivirkningene til at du i enkelte situasjoner unnlater å ta den faste kolesterolsenkende medisinen?
Hvis ja, beskriv i hvilke situasjoner du lar være å ta medisinen
Glemmer du ofte å ta medisinen?

Hva er som oftest grunnen til at du glemmer å ta den?
Har du kolesterolavleiringer (xanthomknuter, xanthelasmer, arcus cornea)?
Hvordan har disse endret seg siste 10 år (etter studien)?
Har du hatt hjertesykdom? (hjerteinfarkt, angina, blodpropp)
Hjertesykdom årstall, diagnose, tiltak
Har foreldrene dine hatt hjertesykdom?
Har du hatt noen andre sykdommer (utenom forkjølelser ol)?
Hvilke medikamenter (medisiner/naturmediiner utenom kolesterolsenkende) bruker du i dag?
Er du student, i jobb, eller ikke i jobb?
Hvor mange år høyere utdanning etter VGS har du? (inkluder hvor mange år du får når du er ferdig med studiet)
Kosthold: forteller dem hva de scoret på Smart Diet og svarer på spørsmål
Når var sist gang du fikk kostholdveiledning?
Hvor mange timer i uka trener du utholdenhet?
Hvor mange timer i uka trener du styrke?
Røyker du, eller har du noen gang gjort det?
Hvor mange røyker du/røykte du om dagen?
Når startet/og sluttet du?
Snuser du?
Hvor lenge har du brukt snus?
Antall alkoholenheter i uka
”Jeg tror at sunn kost og livsstil er minst like viktig som å ta riktig medisin med tanke på FH”
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig
”Jeg spiser sunnere enn jeg ville gjort om jeg ikke hadde FH”
”Jeg synes det er vanskelig å finne kolesterolvennlig mat på offentlige spisesteder”
”Jeg synes det kan skape vanskelige situasjoner når jeg blir servert mat jeg vet ikke er bra for meg i sosiale sammenhenger”
”Jeg føler at FH forringer min matglede”
”Jeg trener/mosjonerer mer enn jeg ville gjort om jeg ikke hadde FH”
”Jeg røyker ikke/sluttet å røyke/røyker mindre pga jeg har FH”
”Jeg skulle ønske jeg slapp å bekymre meg om livsstilen min (pga FH)”
”Jeg føler at jeg burde vært flinkere til å leve sunt”
”Jeg er glad for at jeg er bevisst på å leve sunt”
Anser du din helse som bedre enn gjennomsnittet, gjennomsnittlig, dårligere enn gjennomsnittet?
Bedre enn gjennomsnittet, gjennomsnittlig, dårligere enn gjennomsnittet
Hvis bedre, hvorfor?
Hvis dårligere, hvorfor?
”Jeg bekymrer meg over om jeg kommer til å få hjerteinfarkt (hjertesykdom) pga FH”
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig
”Jeg stoler på at behandlingen min kommer til å forhindre at jeg får hjerteinfarkt (hjertesykdom)”
”Jeg er redd for at den av foreldrene mine som har FH kommer til å bli hjertesyk (igjen)?”
”Jeg er engstelig over tanken på at jeg kan gi (eller har gitt) FH videre til mine barn”
”Det å ha FH har aldri vært noe problem å snakke om I min familie”
”Jeg synes det er vanskelig å fortelle andre om at jeg har FH”
”Jeg skulle ønske at jeg og min familie ikke visste om FH diagnosen”
”Jeg skulle ønske at jeg hadde fått diagnosen om FH senere (som voksen)”
Er det ting i oppfølgningen din som kunne gjort det lettere å leve med FH, hvis så hva da?
Hvor enig/uenig er du I påstanden "jeg er fornøyd med min oppfølgning av FH"
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig
Hva er du mest fornøyd med i din oppfølgning?
Hva er du minst fornøyd med i din oppfølgning?
”Jeg gruer meg til legekonsultasjonene når det gjelder FH”
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig
Hvis ikke Helt Uenig, hvorfor?
”Jeg føler ikke at helsevesenet bør være så pågående når det gjelder FH”
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig
”Jeg ønsker blodprøvekontroll og legeundersøkelse for FH med følgende hyppighet”
4 ganger årlig, 2 ganger årlig, 1 gang I året, sjeldnere
”Jeg føler ikke at jeg får den informasjonen jeg trenger om FH”
Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig

”Jeg føler at det jeg leser/hører om i media stemmer godt overens med det legen min og LK har fortalt meg om kolesterol og kolesterolsenkende medisiner”

Helt enig, Delvis enig, Verken enig eller uenig, Delvis uenig, Helt uenig

”Det hender at medieoppslag gjør meg skeptisk til råd jeg har fått av legen min eller LK om FH behandlingen min”

”Jeg er usikker på hvilke kilder til informasjon om FH jeg kan stole på”

Hva er dine kilder til det du kan om FH?

Informasjon fra studien

kryss av hvis relevant

Lærte av foreldre som barn

Informasjon fra å komme til LK

Informasjon fra fastlegen

FH-foreningen

Andre kilder

Appendix 7: Participation the parent studies

Parent trial(s) participated in	n [1] (%)
Akid	15 (22.4%)
Zink	13 (19.4%)
Plantesterol	13 (19.4%)
Ezi-Simva	3 (4.5%)
Welchol	4 (6.0%)
PLUTO	11 (16.4%)
Plantesterol + PLUTO	3 (4.5%)
Plantesterol + Ezi-Simva	1 (1.5%)
Ezi-Simva + PLUTO	1 (1.5%)
PLUTO + Welchol	2 (3.0%)
Plantesterol + PLUTO + Ezi-Simva	1 (1.5%)

Data are given as n (%)
[1] n indicates number of individuals

Appendix 8: Subjective evaluation of parent study participation

Characteristics	n [1] (%)
Who decided study participation?	
Myself	17 (25.8%)
Parents decided, I agreed	48 (72.7%)
Parents decided, I did not agree	1 (1.5%)
Why did you participate?	
To get better treatment and follow-up	36 (54.5%)
Doctors recommendation	3 (4.5%)
To find a drug I can tolerate	4 (6.1%)
Help with science	11 (16.7%)
Exiting to be involved in a project	2 (3.0%)
To get better treatment and follow up and help with science	9 (13.6%)
Do not know	1 (1.5%)
Did you find it stressful to participate in the study as a child?	
Agree fully	1 (1.5%)
Agree partly	7 (10.6%)
Neither agree or disagree	3 (4.5%)
Disagree partly	13 (19.7%)
Disagree fully	42 (63.6%)
Did you find it positive to have been included in a study?	
Agree fully	56 (86.2%)
Agree partly	3 (4.6%)
Neither agree or disagree	5 (7.7%)
Disagree partly	1 (1.5%)
Disagree fully	0 (0%)

Data are given in n (valid percent)
[1] n indicates number of individuals

Subjective experiences of being included in the parent study/studies

Characteristics	n [1](%)
Did you get something positively out of being involved in the study?	
No	20 (30.8%)
Yes	45 (69.2%)
If yes, what	
N/A	20 (30.8%)
Frequently and close follow-up	7 (10.8%)
Increased knowledge / understanding of the disease	5 (7.7%)
Better cholesterol levels	4 (6.2%)
Dietary advices	8 (12.3%)
Travelling to Oslo	2 (3.1%)
Involved in testing a new medication	3 (4.6%)
Follow-up and increased knowledge	4 (6.2%)
Dietary advices and increased knowledge about the disease	6 (9.2%)
Dietary advices and travelling to Oslo	1 (1.5%)
Dietary advices and follow-up	3 (4.6%)
Generally positive	2 (3.1%)
Did you get something negatively out of being involved in the study?	
No	59 (90.8%)
Yes	6 (9.2%)
If yes, what	
N/A	59 (90.8%)
Side effects of the medication	1 (1.5%)
"Fasting period"	1 (1.5%)
Blood samples uncomfortable	2 (3.0%)
Blood samples uncomfortable and dietary advices	1 (1.5%)
Blood samples uncomfortable and side effects	1 (1.5%)

Data are given in n (valid percent)
[1] n indicates number of individuals
N/A = not applicable