

Mortality and cardiovascular morbidity in patients with familial hypercholesterolemia



PhD Thesis

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UNIVERSITY OF OSLO

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In memory of my dear and always encouraging and inspiring parents Myrthel and Johannes, who both passed away so quickly during my time as a PhD student. I miss you so much, and I think of you every day. I know you would have been proud of me for accomplishing this work.

Oslo, April 2016

Liv J Mundal



Portrait of an Elderly Lady painted by Frans Hals in 1633 (on the previous page). This woman has visible interdigital xanthomas located at the extensor tendons which are pathognomonic for FH. With permission from the National Gallery of Art, Washington, USA.

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SELECTED ABBREVIATIONS

ACS: Acute coronary syndrome

ACME: Automatic Classification of Medical Entities

AMI: Acute myocardial infarction

BMI: Body mass index

BP: Blood pressure

CAD: Coronary artery disease

CABG: Coronary artery bypass graft

CI: Confidence interval

CHD: Coronary heart disease

CVD: Cardiovascular disease

CVDNOR: Cardiovascular Diseases in Norway

FH: Familial hypercholesterolemia

GPs: General practitioners

GCP: Good clinical practice

HDL-C: High density lipoprotein cholesterol

HMG-CoA reductase inhibitors: Hydroxy-methyl-glutaryl-CoA reductase inhibitors (Statins)

ICD: International Classification of Diseases

IHD: Ischemic heart disease

IMT: Intima-media thickness

LDL-C: Low density lipoprotein cholesterol

Lp(a): Lipoprotein (a)

MI: Myocardial infarction

NCMP: The NOMESCO classification of medical procedures

NCoDR: The Norwegian Cause of Death Registry

NCSP: The NOMESCO classification of surgical procedures

NSTEMI: Non-ST elevation myocardial infarction

PAS: Patient Administrative Systems

PAD: Peripheral arterial disease

PCI: Percutaneous coronary intervention

PCSK9: Proprotein convertase subtilisin/kexin type 9

PVD: Peripheral vascular disease

REK: Norwegian Regional Committee for Medical and Health Research Ethics

SCD: Sudden cardiac death

SMR: Standardized mortality ratio

SSB: Statistics Norway

STEMI: ST-elevation myocardial infarction

SIF95: Norwegian classification of medical procedures; 3rd edition, 1995.

TG: Triglycerides

TC: Total cholesterol

UCCG: The Unit for Cardiac and Cardiovascular Genetics

WHO: World Health Organization

LIST OF PAPERS

Paper I

Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierød MB, Leren TP, Retterstøl K. Mortality among patients with familial hypercholesterolemia: A registry-based study in Norway, 1992-2010. *J Am Heart Assoc* 2014;3:e001236.

Paper II

Krogh HW, **Mundal L**, Holven KB and Retterstøl K. Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. *Eur Heart J* 2015;doi: 10.1093/eurheartj/ehv602.

Paper III

Mundal L, Veierød MB, Halvorsen T, Holven KB, Ose L, Iversen PO, Tell GS, Leren TP, Retterstøl K. Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994-2009, a registry study (submitted).

Paper IV

Mundal L, Igland J, Ose L, Holven KB, Veierød MB, Leren TP, Retterstøl K. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013 (submitted).

Introduction

Familial hypercholesterolemia

Background and status of knowledge

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder characterized by high low-density lipoprotein-cholesterol (LDL-C) which leads to an increased risk of premature cardiovascular disease (CVD) due to early atherosclerosis (1, 2). FH is one of the most frequent hereditary disorders (3), known to cause premature coronary heart disease (CHD) due to atherosclerosis in the coronary arteries (4) as shown in Figure 1. If not adequately treated, approximately 85% of males and 50% of females with FH will suffer a coronary event before age 65 years (5). A 20-fold increase in the incidence of myocardial infarction (MI) in middle age has been reported in FH patients due to elevated cholesterol-levels (6).

Most often FH is caused by mutations in the LDL-receptor gene which leads to a defect or absent LDL-uptake (1, 5, 7).

The first patients with xanthomatosis and CVD were described in late 18th century (8). During 1925-1938, the Norwegian pathologist Francis Harbitz published several reports on sudden death and xanthomatosis (8). In 1937 FH was described by Professor Carl Müller in Norway who found the link between xanthomatosis, hypercholesterolemia and CHD (8). Based on his studies he postulated that causal and prophylactic treatment might prove to be of value (8). In 1973 the LDL-receptor and its importance for the cellular uptake of LDL-C was discovered by Brown and Goldstein who won the Nobel Prize in 1985 (6, 9). The understanding of LDL-C uptake in relation to the activity level of the LDL-receptor was essential (6). During the 1980s-1990s the first cholesterol-lowering treatment with hydroxymethyl-glutaryl-CoA (HMG-CoA) reductase inhibitors known as statins were introduced and became the first line treatment in FH (6). Statins is associated with improved CVD outcome. In 1994 the Scandinavian Simvastatin Survival study was the first evidence that long-term treatment with statins significantly improved survival in all patients with CHD by decreasing the LDL-C level (10). In Norway, the Lipid Clinic at Oslo University Hospital (formerly

Rikshospitalet) was founded by Leiv Ose in 1984, and recently the National Advisory Unit on FH was established (11).

There is a homozygous and a heterozygous form of FH, of which the homozygous form is the most severe affecting about 1:160 000-1:300 000 (7, 12, 13). If left untreated, CVD typically occurs early in life (12). Long-term exposure to elevated LDL-C from birth leads to early ischemic heart disease (IHD) in childhood or early adulthood in homozygous, and in mid adulthood in heterozygous FH (14). Heterozygous FH is less serious and more common than previously believed, with a prevalence of 1:200-1:217 (15, 16). Based on this prevalence, it is expected that about 35 million people globally have FH, of which > 23 000 individuals in Norway (17). However, the majority of FH patients is still underdiagnosed and undertreated (15). Although Norway has the second highest percentage of genetically diagnosed FH worldwide, next after the Netherlands, < 1/3 of all individuals expected to have FH in Norway are currently diagnosed (15).

In Norway, there is a National patient registry for all individuals with genotyped FH which consists of > 6500 FH patients, of which the majority have heterozygous FH. According to the World Health Organization (WHO) a patient registry is a file of documents containing uniform information about individual persons collected in a systematic and comprehensive way, in order to serve a pre-determined purpose (18). The combination of the large number of genotyped FH patients in Norway with a complete follow-up, and the possibility to link these data to other national health registries has offered a unique opportunity that can only be done in Norway at present.

In most FH patients high LDL-C levels can be normalized by cholesterol-lowering treatment. As high LDL-C is the triggering cause for CVD, it is commonly accepted that a reduction of LDL-C is important. However, modern treatment of FH is inadequately documented on hard endpoints such as MI or cerebral ischemic stroke as there are no controlled randomized studies on hard endpoints in FH patients, and placebo-controlled studies cannot be conducted for ethical reasons. Clinical management is therefore largely based on extrapolation of results of cholesterol-lowering trials in hyperlipidemic patients in the general population (19). National FH patient registries are therefore important in order to follow large FH cohorts over time to study diagnostics, treatment and follow-up of FH

patients from childhood and onwards to assess their risk of morbidity and mortality compared with the corresponding general population.

The purpose of this PhD thesis

To date, important data have been missing for answering questions about how modern cholesterol-lowering treatment affects mortality, morbidity and the prognosis for individuals with FH. The purpose of this thesis was to study a complete cohort of all Norwegian genotyped FH patients with various mutations regarding sex and age-specific mortality and CVD morbidity compared with the general population, further to generate new knowledge on the role of elevated LDL-C (by a genetic cause) for the development of premature CVD and to describe health status in a complete cohort of Norwegian FH patients. This thesis is very much about how CVD and CHD in particular can be prevented in patients with a very high CVD risk, and the results may therefore have a great importance for public health. Apart from individuals with FH, many other patients in the general Norwegian population taking cholesterol-lowering medication to prevent CVD may benefit from the results.

The link between cholesterol and cardiovascular disease

Cholesterol is essential for life, a necessary component of all cell membranes, and important for the biochemical foundation of all steroid hormones and the bile acid biosynthesis (20). The LDL-C particle consists of cholesterol, phospholipids and apolipoprotein B-100 at the surface, and carries cholesterol throughout the body (20). The LDL-C is extracted from blood by use of LDL-receptors located in the liver at hepatic cells as shown in Figure 2, and plays an important role in the cholesterol metabolism (21). High circulating LDL-C contributes to atherosclerosis which is accumulations of fatty deposits inside the arteries leading to narrowing of the vessel lumen, triggering the formation of blood clots and clot obstructions ultimately causing ischemia and end organ damage such as CHD and MI due to occlusions in the coronary arteries (Figures 1 and 9). As FH leads to a high circulating LDL-C due to LDL-receptor deficiency from birth, the endothelium in the blood vessels will be exposed to high LDL-C values for several years during childhood (1), prior to debut of clinical symptoms. It has been reported that the process of atherosclerosis is initiated in early childhood in FH patients which predisposes to premature CVD (22). By ultrasound examinations of the carotid

arteries, a difference in mean intima-media thickness (IMT) in the FH children compared with unaffected siblings may be significant as early as age 8 years (22).

Figure 1. Cardiovascular disease due to cholesterol deposits in the arteries

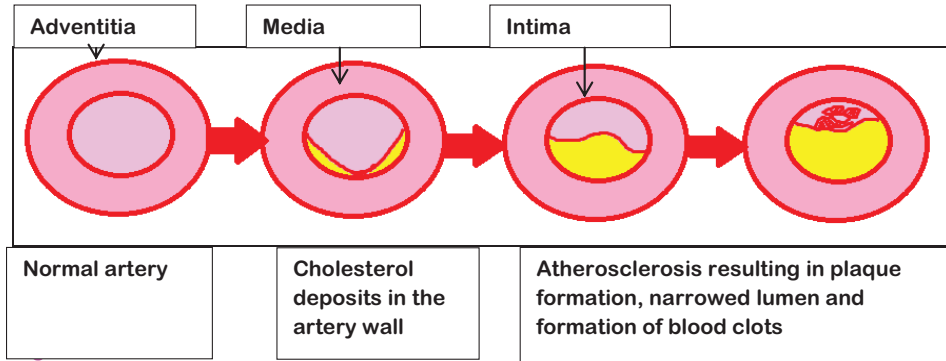


Figure 1 shows a cross-section of arteries from a normal artery with normal blood flow to the left to a gradually narrowed artery lumen with plaques buildups due to atherosclerosis, and ultimately occluded artery to the right. The artery wall is divided into three parts consisting of adventitia, media and intima. **Source: Liv J Mundal, the Lipid Clinic, Oslo University hospital**

The genetics of FH

FH is mainly caused by mutations in the gene encoding the LDL-receptor (1). Defective LDL-receptors leads to a reduced LDL-C uptake in the hepatic cells (6) as shown in Figure 2. More than 1 700 different mutations in this gene have been demonstrated in different families with FH worldwide (23). Currently, about 225 different mutation types are registered in Norway (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital), of which four mutations are responsible for 47.2% of all FH cases in Norway (24). Another cause of FH is a mutation in the gene for apolipoprotein B (APOB), which is the main protein in the LDL particle (25). Mutations of the APOB gene interfere with binding of the LDL particle to the LDL-receptor, and result in elevated LDL-C (14) (Figure 2). Further, FH can be caused by a mutation in the gene that codes for the enzyme proprotein convertase subtilisin / kexin type 9 (PCSK9) which is involved in the degradation of the LDL-receptor (6). PCSK9 protein binds to the LDL-receptor and increase the degradation of the LDL-receptor-LDL-C complex, which reduce the recycling of the LDL-receptor and the number of available LDL-receptors on the surface of the hepatic cells (14), as shown in Figure 2. In Norway mutations in the LDL-receptor gene is most frequent

(97%) compared to mutations in the APOB gene (2%) and PCSK9 gene (1%) (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital).

The level of activity of the LDL-receptor affects the LDL-C values measured in the patients depending on the site of the mutation in the LDL-receptor gene (6). In heterozygous FH the normal activity level of the LDL-receptor is reduced by 50% while in homozygous FH the LDL-receptor activity level varies from 5 to 25% of normal activity to more or less no functional LDL-receptors (6).

Figure 2. Different mutations in Familial Hypercholesterolemia

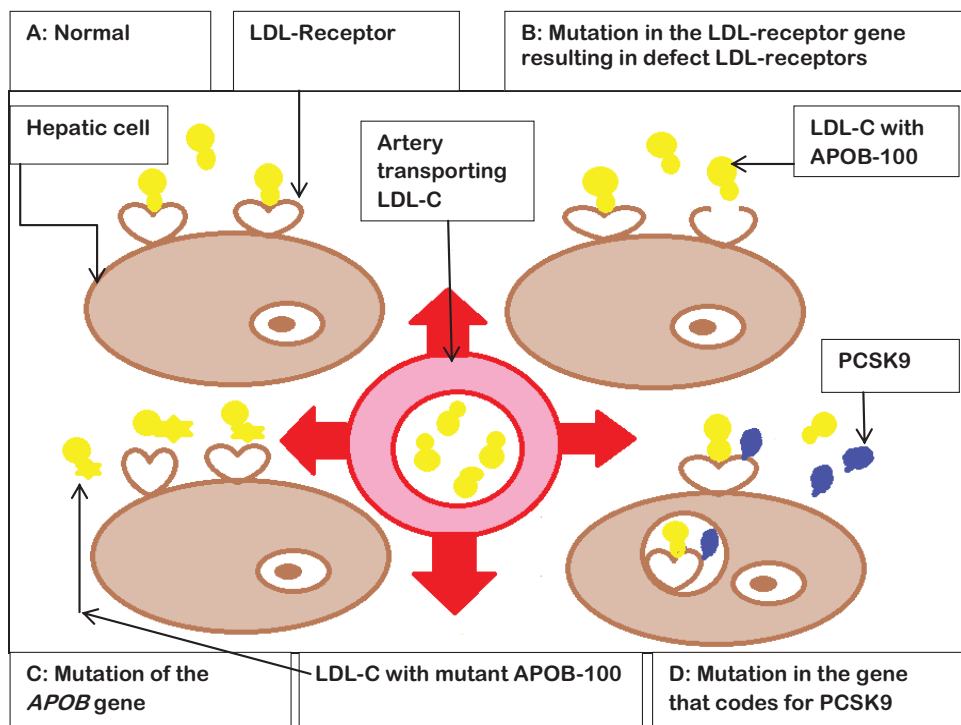


Figure 2 shows A: normal function with binding of the LDL-C to the LDL-receptor on the surface of the hepatic cell, B: shows a defect LDL-receptor which makes it impossible for the LDL-C to bind to this receptor, C: shows how mutations of the APOB-100 impairs the ability of the APOB to bind to the LDL-receptor due to a changed structure, D: shows how PCSK9 binds to the LDL-receptor and how the entire complex consisting of PCSK9, LDL-C and LDL-receptor is integrated in the hepatic cell. The LDL-receptor is degraded and subsequently the LDL-receptor recycling to the cell surface is prevented resulting in reduced numbers of LDL-receptors.

Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

How to diagnose FH

The FH diagnosis can be based on genotyping or on a clinical diagnosis. In Norway, genotyping is performed at the Unit for Cardiac and Cardiovascular Genetics (UCCG) at Oslo University Hospital. Most patients want to take a genetic test in order to achieve the greatest possible diagnostic accuracy (26). In less than 1% of all cases there are undiscovered mutations in the LDL-receptor gene (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital). When the underlying mutation in the LDL-receptor gene has been identified in an index patient, molecular genetic screening of first degree relatives has a very high sensitivity and specificity close to 1.0 (3). About 15-30% of FH cases may be classified incorrectly if only a clinical diagnosis is used compared to a genetic test (3).

A clinical FH diagnosis in adults with heterozygous FH is based on clinical tools assessing the probability of having FH by use of clinical and laboratory findings such as the Dutch Lipid Clinic Network criteria. This tool uses a scoring systems combining the plasma level of LDL-C, clinical signs, family history of CHD, and molecular genetic testing (15), as shown in Table 1. A definite FH diagnosis can be made if the individual scores >8 points, a probable diagnosis if the subject scores 6-8 points, and a possible diagnosis if the individual scores 3-5 points (15). Apart from the Dutch Lipid Clinic Network criteria, there are also other clinical tools for diagnosing FH such as the UK Simon Broome criteria (27, 28), or other tools. No international consensus exists on which set of criteria is superior, but the Dutch Lipid Network Clinic criteria are endorsed by many guidelines, such as the European Society of Cardiology (ESC) (15, 29) and is the one used in this thesis.

Once established a FH diagnosis in an individual, cascade screening of close relatives is recommended as shown in Figure 3 to give optimal disease prevention. Cascade screening involves identifying people at risk for a genetic condition by a systematic screening of close biological relatives of an index patient (4). It is important to track potential undiagnosed relatives in order to establish a FH diagnosis as FH may be present in 50% of first degree relatives (30).

Figure 3. Cascade screening of family members of an index patient

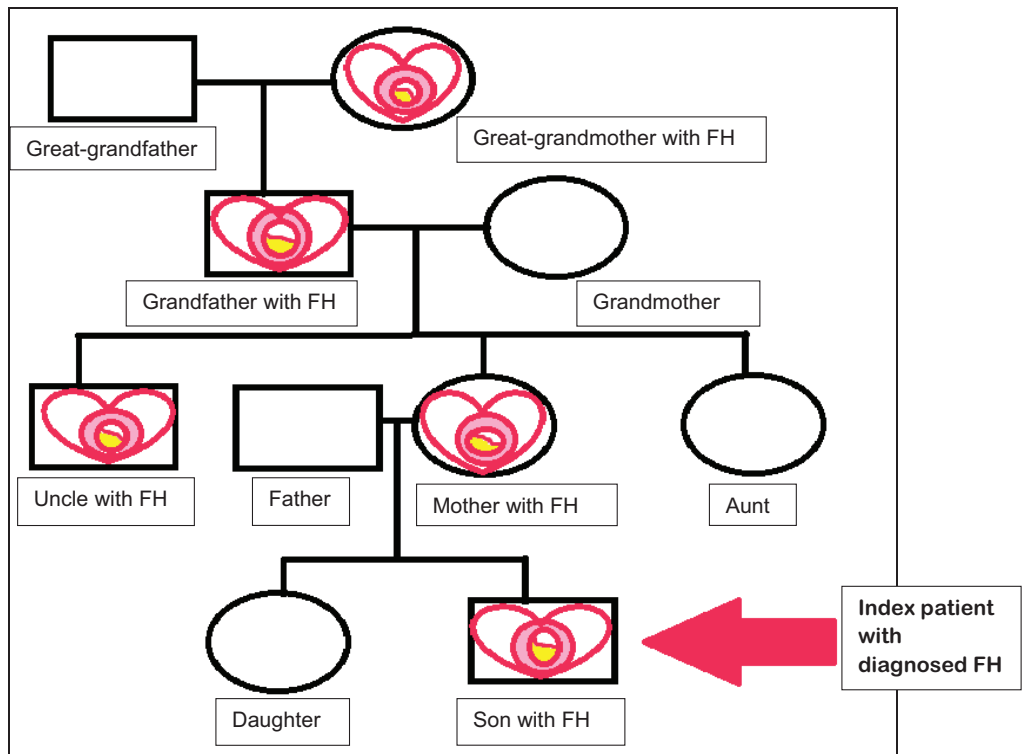


Figure 3 shows how FH, which is an inherited disease, can be transferred to new generations and can be traced back to earlier generations within the same families.

Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Currently, there is no specific diagnostic code for patients with established FH in the International Classification of Diseases, 10th Revision (ICD-10). The ICD-10 code: E.78.0, pure hypercholesterolemia, is used both for FH besides other forms of hypercholesterolemia which may lead to misclassifications and under-reporting of FH.

Before confirming a FH diagnosis, secondary causes of hyperlipidemia should be excluded which includes hypothyroidism, nephrotic syndrome, obstructive liver disease, and diets with extremely elevated saturated fat/cholesterol content (14). It is important to secure that the liver enzymes, renal function and thyroid hormones are normal and that there are no albuminuria and hyperglycemia present (15).

Table 1. Dutch Lipid Clinic Network criteria for diagnosis of heterozygous FH in adults

<u>Group 1: Family history</u>	Points
(I) First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD) OR	1
(II) First-degree relative with known LDL cholesterol >95th percentile by age and gender for country	1
(III) First-degree relative with tendon xanthoma and/or corneal arcus OR	2
(IV) Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender for country	2
<u>Group 2: Clinical history</u>	
(I) Subject has premature (<55 years, men; <60 years, women) CHD	2
(II) Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
<u>Group 3: Physical examination</u>	
(I) Tendon xanthoma	6
(II) Corneal arcus in a person <45 years	4
<u>Group 4: Biochemical results (LDL cholesterol)</u>	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
<u>Group 5: Molecular genetic testing (DNA analysis)</u>	
(I) Causative mutation shown in the <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i> genes	8

Source: Reprinted with permission from Børge G. Nordestgaard. Modified from Nordestgaard BG et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90a(15).

Clinical symptoms and manifestations

A high LDL-C from birth gives an increased risk of developing premature atherosclerosis in the vessel wall and lipid depositions in other tissues, such as tendon xanthomas, xanthelasma around the eyes and arcus cornea in the limb of the cornea (6) as shown in Figure 4. As many FH patients are asymptomatic, thus not aware of having FH, the detection of subclinical atherosclerosis is vital and should be actively sought (5). CVD manifestations in FH patients may be asymptomatic or symptomatic. Symptomatic manifestations of atherosclerosis leading to CHD may be present as angina or MI, cerebrovascular symptoms as stroke, or peripheral artery disease (PAD) as claudication. PAD is more frequent in FH patients compared to sex and age matched controls (31, 32). In a study of heterozygous statin treated FH patients, of whom 91% had genotyped FH and 89% were on statins, PAD was present in approximately one in five patients and was asymptomatic in almost 60% compared to normolipidemic controls (32). Accordingly routine screening in FH patients is recommended, even if asymptomatic (32).

If left untreated, clinical symptoms of CVD typically manifest in men in their fourth decade and in women in their fifth decade of life. However, there is considerable variation in age at onset of CVD and in presence of various clinical symptoms in heterozygous FH patients, even among carriers of an identical mutation where the clinical manifestations may or may not be present (5, 33, 34). Further, type of FH such as homozygous or heterozygous form is vital for the debut age of clinical signs. While xanthomas are considered pathognomonic for FH, the xanthelasma and arcus cornea are not (35). Tendon xanthomas are associated with a three times higher risk of CVD in individuals with FH suggesting that xanthomas and CVD may share etiology (36). The prevalence of tendon xanthomas in heterozygous FH patients is about 7% at age 20-30 and 32 % at age 41-50 years, and overall present in 30-50% of all genetically verified heterozygous FH patients, significantly associated with the LDL-C level (37), indicating a need for aggressive lipid-lowering intervention (37). Furthermore, there seems to be a significant positive association with tendon xanthomas and age, male sex and hypertension (37).

Figur 4. Clinical manifestations in FH patients

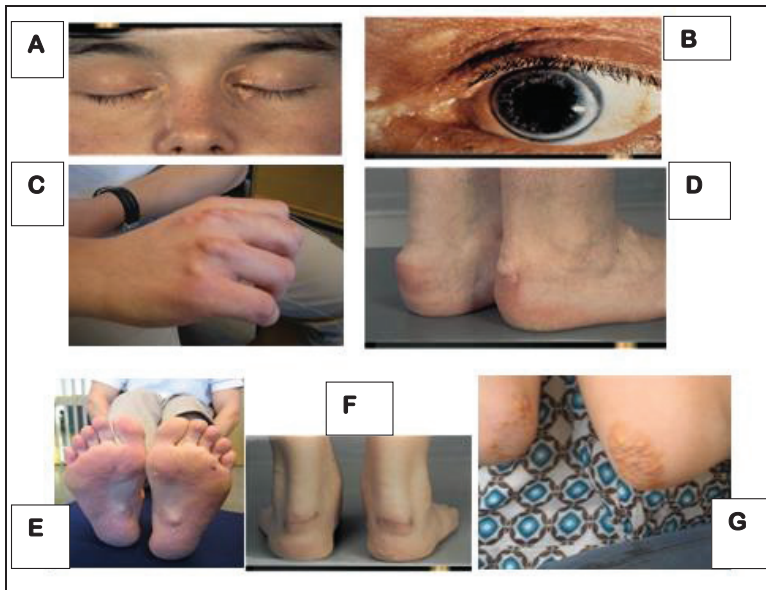


Figure 4 shows A: xanthelasmas near the inner canthus of the eyelid, B: arcus cornea in the corneal margin, C: hand extensor tendon xanthomas around the metacarpophalangeal joints, D and F: achilles tendon xanthomas, E: plantar xanthomas, and G: eruptive xanthomas on the elbows.

Source: Photos taken by Leiv Ose with patients' consent, modified and printed with permission.

The CVD risk factors

Apart from high LDL-C from birth, other CVD risk factors and interaction with environmental factors is of importance (38). The risk of CVD is multifactorial related to lifestyle, lack of physical activity, tobacco smoking, dietary habits, hypertension, diabetes, low HDL-C, male sex, increasing age body mass index (BMI) and family inheritance (39). As in the general population the risk of most CVD conditions are higher in presence of family history (45% higher odds with sibling history), i.e. stroke (50% higher odds with first degree relative history), and for atrial fibrillation, heart failure and PAD there is 80%, 70% and 80% higher odds with parental histories, respectively (40). In heterozygous FH patients the major CVD risk factors reported are given in Figure 5. The earliest possible identification of risk factors is of vital importance to prevent premature CVD in FH patients.

Figure 5. Major CVD risk factors in FH patients

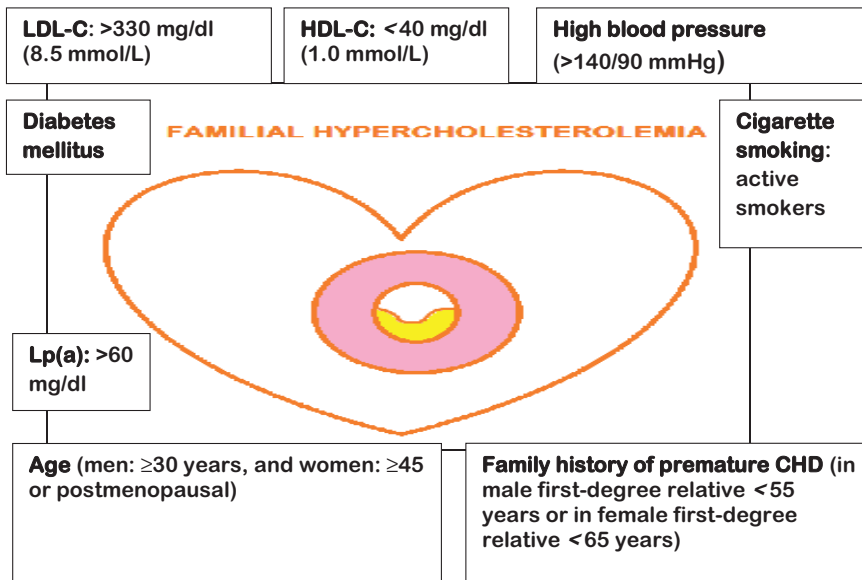


Figure 5 displays the major CVD risk factors in heterozygous FH
Source: Modified from Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;173:55-68(5).

Primary and secondary prevention

It is commonly accepted that reduction of LDL-C will reduce the risk for CVD (41). There is a linear relationship between reduction in LDL-C and reduction in the risk for major CVD events of which every 1 mmol/L reduction in LDL-C gives a corresponding 22% reduction in CVD events (19, 39) which should urge physicians to obtain recommended LDL-C targets for primary and secondary prevention in FH patients according to established treatment guidelines (39).

Statins are the first-line treatment for reducing LDL-C, and is of similar effectiveness for prevention of CVD in men and women with equivalent CVD risk (42). Apart from statins, diet therapy with a low content of saturated fat and a regular intake of fish, fruits, vegetables, and whole grains, and beans should be encouraged (43). Further, alcohol intake should be moderate, and regular physical exercise recommended (43). Dietary supplements with plant sterols may be used to incrementally lower plasma LDL-C (43). Major present CVD risk factors should be addressed in FH patients as shown in Figure 5.

In primary prevention an LDL-C < 2.5 mmol/L is recommended (15, 39). In secondary prevention an LDL-C level of < 1.8 mmol/L is recommended in patients with established CVD or in patients with diabetes or in previously untreated individuals > 40 years of age (15). An early and optimal preventive treatment in FH patients with a reduction in LDL-C levels to target values in young adulthood is important in order to reduce the risk of premature CVD. Unfortunately, many FH patients fail to achieve the treatment targets for LDL-C for various reasons such as reduced LDL-receptor function, high baseline values of LDL-C, non-sufficient treatment doses and reported side effects on statins or other cholesterol-lowering pharmaceuticals leading to intolerance and reduced patient compliance (7, 15, 44). In the Danish population study, only 48% of the FH patients received statins, indicating a severe under treatment of FH patients (2).

To reduce the risk of adverse effects of statins, physicians must be aware of specific patient characteristics, such as advancing age, sex, BMI, or glomerular filtration rate which may predict musculoskeletal and hepatic toxicity (44). Overall, low rates of serious side effects have been observed with high-dose statin therapy (44). Apart from cholesterol-lowering medications, LDL apheresis is an important treatment option in homozygous FH, or in severe heterozygous FH where multiple pharmaceuticals are inadequate (45), or in FH women with established CVD not able to use pharmaceuticals during pregnancy (5).

It is not evident how early in life FH patients should start on statins (46). It has been demonstrated by ultrasound examination of the carotid arteries by measuring the IMT in the vessel wall that progression of atherosclerosis may be delayed or possibly reversed by good control of LDL-C in children at 10 years of age (41, 46). The exposure to hyperlipidemia in young adulthood will affect future CHD risk in a dose-responsive manner (47). Optimal preventive treatment is important and should be initiated preferably before the atherosclerotic plaques develop (6).

Pharmaceutical therapy

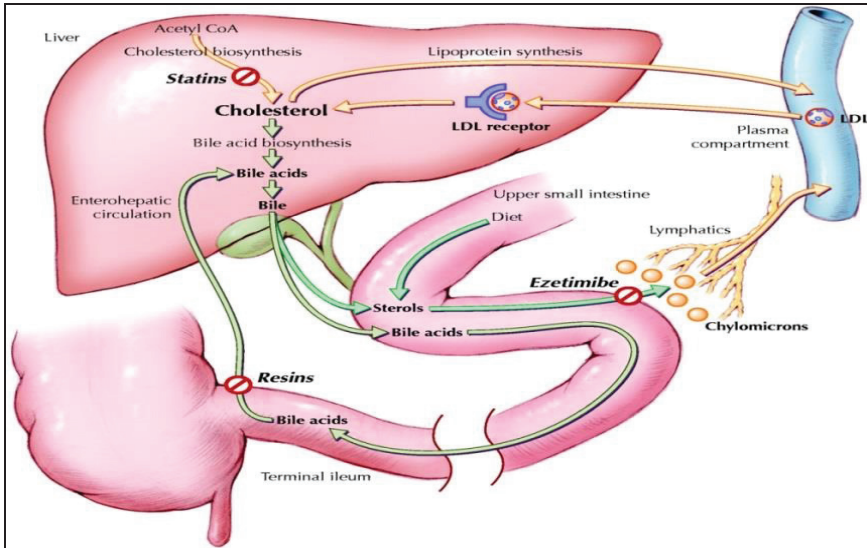
Currently, the major LDL-C lowering agents available in Norway are statins, selective inhibitor of the absorption of cholesterol from the intestine (ezetimibe), bile acid sequestrants (resins), and PCSK9-antibodies. Statins competitively inhibits the rate-regulatory step in the endogenous cholesterol synthesis by inhibiting the HMG-CoA reductase activity in the liver,

which increases the extraction of LDL-C from the circulation by increasing the numbers of LDL-receptors at the hepatic cells (6, 39) as shown in Figures 2 and 6. Statins are recommended as first-line therapy in all FH patients and reduces LDL-C by up to 50% with high intensity treatment (48). By use of statins, CVD morbidity and mortality is reduced by approximately 30-45% (49). Irrespective of sex, statins are of similar effectiveness at an equivalent risk of CVD (42). By every 1 mmol/L reduction in LDL-C, statins give a reduction in all-cause mortality by 9% and 22% in CVD events by reducing vascular events by about 20%, major coronary events and coronary revascularizations by 25% and stroke by 15% (42).

However, monotherapy with statins may be inadequate to reach the LDL-C targets. Additional therapy with other pharmaceuticals may often be necessary, such as ezetimibe or other lipid lowering agents. Ezetimibe reduces LDL-C by about 15-20% when given as monotherapy (49). When added to statins additional reduction in LDL-C by 15-20% is reported (39), as well as improved CVD outcomes such as CVD deaths, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke (50). Other pharmaceuticals are bile acid sequestrants (resins) which bind bile acids in the gut and inhibit re-absorption as shown in Figure 6. By use of resins a LDL-C reduction up to 25% has been observed (39).

New promising cholesterol-lowering pharmaceuticals have recently been available, such as a monoclonal antibody that inhibits PCSK9 as shown in Figure 7 which significantly reduces LDL-C about 60% in patients already on maximum statin treatment (6, 45, 51). By use of PCSK9-antibodies, it is expected that > 80% of all patients will reach target values for LDL-C (52).

Figure 6. Cholesterol-lowering pharmaceuticals and site of action



Source: Francis GA, Johnson RL, Findlay JM, Wang J and Hegele RA. Cerebral cholesterol granuloma in homozygous familial hypercholesterolemia. CMAJ 2005;172:495-7(21). Reprinted with permission.

Figure 7. Monoclonal antibody that inhibits PCSK9

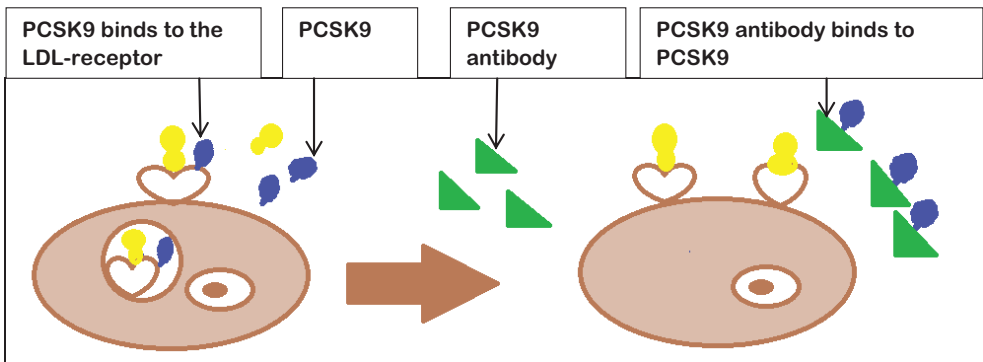


Figure 7 shows how PCSK9 antibody binds to PCSK9 preventing PCSK9 binding to the LDL-receptor resulting in a normalized receptor function activity on the surface of the hepatic cell.
Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Cardiovascular disease epidemiology

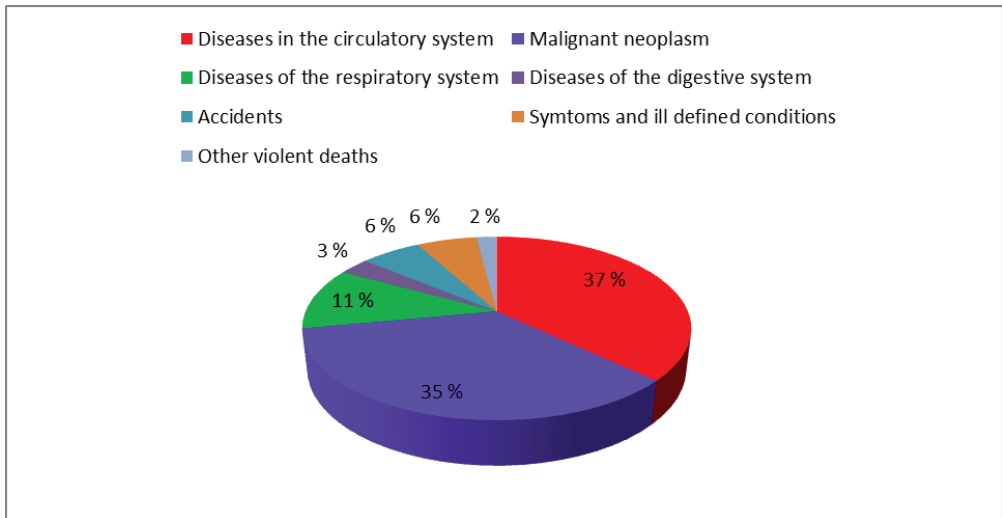
CVD mortality and morbidity in the general population

CVD is the leading cause of death worldwide accounting for about 30% of all annual deaths (53, 54). Globally, IHD and stroke are the two most common death causes (55). Although the age-standardized death rates (per 100 000) has declined by 21% globally during 1990-2010, (55) there has been an increment in the age-standardized deaths rates for atrial fibrillation/atrial flutter by about 90%, and for peripheral vascular disease (PVD) by 53% during the same time period (55).

The mortality rates due to CVD have decreased in most European countries, but CVD is still responsible for 45% of all deaths, of which 49% of all deaths in women, and 40% of all deaths in men, respectively equating to > 4 million annual deaths (53). The number of CVD deaths increases with age (53). CVD deaths currently accounts for about 35% of all premature deaths < 75 years and 29% of all premature deaths < 65 years of age in Europe (53), where about 20% of all CVD deaths are due to CHD, and 11% are due to cerebrovascular disease (53). In Norway CVD accounted for 37% of all deaths in 2010 (Figure 8), of which IHD was the most common cause of death (56), followed by cerebrovascular disease (ischemic stroke or intracerebral bleeding) (57), which is frequent cause of serious disability affecting about 10 000-11000 people annually (58). Apart from CHD and cerebrovascular disease (stroke included), PAD are major contributors to CVD morbidity (39).

The level of number of deaths, and age and sex specific mortality rates give information of the burden of CVD (59). As shown in Tables 2-4, the age and sex standardized CVD death rates have decreased in Norway both in women and men as in most western European countries. In Norway mortality due to acute myocardial infarction (AMI) has decreased by 80 % in individuals 35-74 year of age (both sexes included) during 1970- 2008 (60).

Figure 8. Causes of deaths in the general Norwegian population

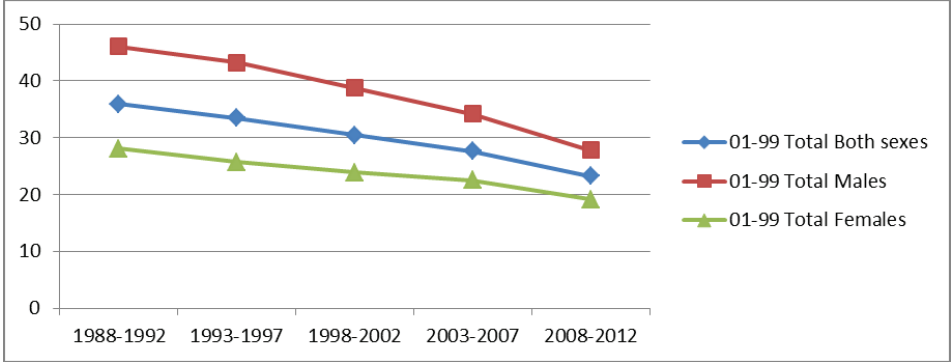


Source: Liv J Mundal, based on data from Statistics Norway 2010. Diseases in the circulatory system (CVD) are defined as ICD-10 codes I00-I99.

Reduction in coronary mortality may be explained by improved prevention and treatment options (61) such as more healthy diets, reduction in smoke, cholesterol-lowering medications, improvement in medical equipment and diagnostics with early invasive strategy and treatment (60). As a result, total in hospital mortality after AMI have been reduced from 15 % to about 5 to 6 % during 1991-2011 (62, 63).

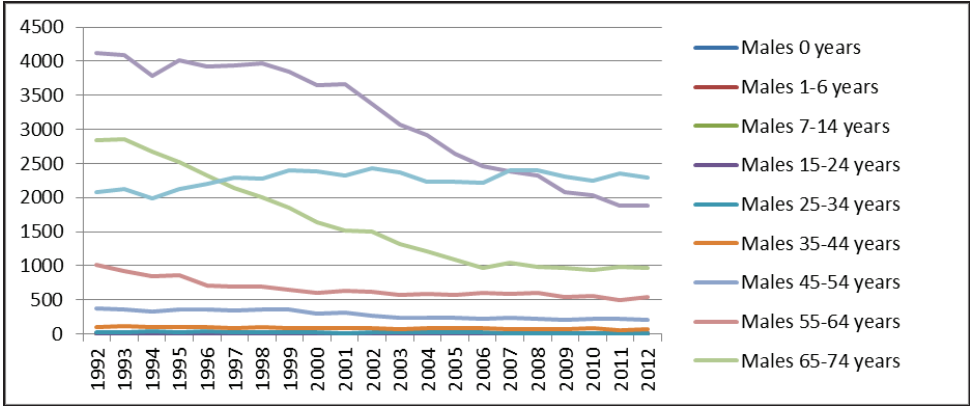
Further, there are reported differences in mortality rates in relation to type of MI, of which ST elevation myocardial infarctions (STEMI) gives the most favorable outcome (64). The non-ST elevation myocardial infarctions (NSTEMI) patients are somewhat older (60). However, there seems to be no significant differences in 30-day mortality in women and men following an acute event, (65) or sex differences in clinical endpoints up to five years in patients undergoing percutaneous coronary intervention (PCI) adjusted for age and comorbidity (66).

Table 2. CVD deaths* in Norway. Age- and sex standardized rates (per 100 000 inhabitants), by sex, cause of death, time and contents



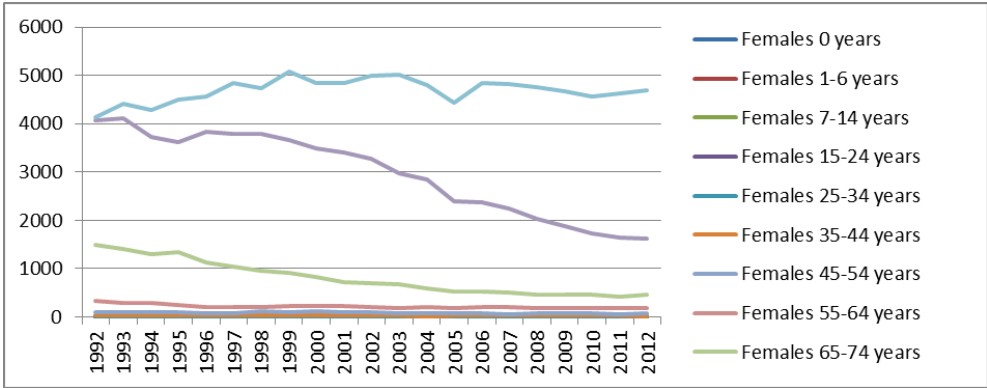
Source: Statistics Norway, modified by Liv J Mundal. CVD deaths are defined as ICD-10 codes I00-I99*.

Table 3. Number of CVD deaths* in men during 1992-2012 in Norway



Source: Statistics Norway, modified by Liv J Mundal. CVD deaths are defined as ICD-10 codes I00-I99*.

Table 4. Number of CVD deaths* in women during 1992-2012 in Norway



Source: Statistics Norway, modified by Liv J Mundal. CVD deaths are defined as ICD-10 codes I00-I99*.

Globally CVD produces a considerable health and economic burden (40). The burden of CVD morbidity on the health care system is reflected in the hospital discharge data based on the incidence and prevalence of CVD (53). Despite decreases in CVD mortality rates in most European countries (Norway included) hospitalizations for CVD have tended to trend upwards since the early 2000s (53, 67). Most CVD hospitalizations are acute admissions (68).

In Norway, CVD is the most common cause of all hospitalizations, of which CHD dominates (69). Women develop CHD on average 10 years later than men (42). Due to CHD, about 12 000-15 000 Norwegians suffer annually from MI (Figure 9) (57), of whom 37 % are women (62, 68, 70). In the Norwegian population in 2013 mean age at the time of the MI was 68.1 years for men and 75.9 years for women (70). About 30% of all MIs are classified as STEMI and 70% as NSTEMI (70), of which 35% of all NSTEMIs and 77% of all STEMIs were invasively treated with PCI (70). In 5.4% of all cases the patients are transferred for coronary artery bypass graft (CABG) surgery (71).

Total number of in-hospital CVD procedures, cardiovascular surgery included, have increased by 28% during 2000-2010 (40). However, since 2005 the rates for surgical-based interventions with CABG declined by about 30% in favor of PCI (53). Apart from surgical and invasive procedures, preventive treatment with statins have led to increased survival rates after MI and reduced risk of new coronary events (62), in addition to antithrombotic

medications (60, 72, 73). Today, most patients are discharged after few days after an AMI (72).

From 1991 to 2000, the number of hospital admissions for AMI in Norway declined by 18%, but from 2000 to 2002 AMI admissions increased by 33% (74), which was mainly due to the changes in the diagnostic criteria for AMI with the introduction of cardiac troponins. Moreover, there was an increment of patient transfers between hospitals due to higher number of coronary invasive procedures because of AMI (74, 75). The AMI event rates were stable during 1994-2002, and then declined annually during 2002-2009 with an average of about 2% in both sexes (76).

Figure 9: An acute myocardial infarction

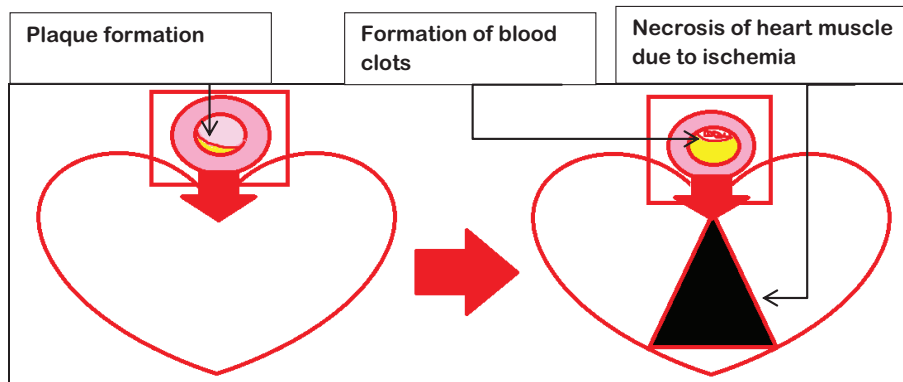


Figure 9 shows atherosclerosis in a coronary artery resulting in plaque formation, narrowed lumen and formation of blood clots ultimately causing ischemia, resulting in an acute myocardial infarction (AMI) and end organ damage.

Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Life expectancy

During 1990-2010 global male and female life expectancy at birth increased from 62.2 to 67.0 in males, and from 68.1 to 73.3 in females (59). In Western Europe corresponding male life expectancy was 72.9 in 1990 and 77.9 in 2010 and 79.4 and 83.2 years in females, respectively (59). In Norway life expectancy increased from 73.6 to 78.5 years in males and from 80.0 to 83.1 years in females in the same time period (59). In Norway in 2013 life expectancy at birth was 79.8 years for men and 83.8 years for women (53). An increment in birth life expectancy has resulted in an increasing number of deaths at older ages (59).

CVD mortality and morbidity in FH patients

FH is associated with reduced life expectancy due to premature CVD (5). Many FH patients will develop premature coronary events (14) which leads to a high CHD mortality in young adults (33, 77). Untreated about 85% of FH men and 50% of FH women will suffer from a coronary event before age 65 years of age (5), and these patients have approximately 20 times the risk of developing coronary artery disease (CAD) compared with the general population (30). The majority of men and women will have symptomatic CHD by 60 years, of which 50% of the men and 15% of the women will have died (39).

The prevalence of CHD in FH patients varies according to age, clinical or genetic FH diagnosis, and CHD subtype. Further, there are differences between countries and in presence of founder effects. The prevalence varies from 1.3% in genotyped FH patients with AMI (78) to 9% in a population with strong founder effect such as in North Karelia in Finland (77). The prevalence of CHD in FH patients is inversely related to age affecting 1:5 in those with CHD < 50 years of age in both sexes (79). Annually, it has been estimated that FH patients account for 5% of all MIs in patients < 60 years (80). In studies with clinical diagnosis of FH the prevalence of CHD varies according to different diagnostic tests, and phenotypic manifestations of FH. In a European cohort study of 4 778 patients with acute coronary syndrome (ACS) with clinical FH according to the Dutch Lipid clinic criteria, the prevalence of probably or definite FH was 1.6%, and possible FH was 17.8% (29). The corresponding prevalence of ACS in men < 55 years of age and women < 60 years of age was 4.8% and 47.1% respectively (29). In patients with premature CAD (< 60 years of age) admitted to a coronary care unit with clinical FH, the prevalence of probable or definite FH was 14.3% (81). In the Danish population study there was a 33% prevalence of CAD in clinical diagnosed FH patients (2). In patients with established CAD the prevalence of PVD is 50% (31). In statin treated heterozygous FH patients (mean age 45.8 years) hemodynamic significant PVD was present in about 30% of all patients (31), and the risk of PVD was nearly 10-fold increased compared with age and sex matched normocholesterolemic control subjects (31). There seems to be no sex differences in age and onset of PVD (31).

Previous studies on mortality and CVD morbidity by use of FH registries

Prior studies on mortality and CVD morbidity are mostly based on clinical FH. The characteristics and summary of study results of previous FH studies by use of FH registries are presented in Appendix in Table A1.

In the pre-statin era, a Danish family study during 1943-1964 in 181 patients with clinical FH reported a 2.18 higher death rate than of normocholesterolemic individuals in the general population (82). The majority (51.6%) died of CHD, followed by sudden deaths without previous known heart disease (16,1%) (82).

CHD deaths were reported in a Japanese study during 1976-1986 based on autopsy studies and hospital records in 527 clinically diagnosed heterozygous FH patients (83). CHD death was the main cause of death in 73.2% of all deaths, of which 48.8% were due to MI and 22.0% were due to sudden deaths (83). Rates of deaths due to CHD was about 11 times higher in heterozygous FH compared with the general population (83). No significant differences were observed in deaths due to cerebrovascular disease (83). In this study mean death age was reported to be significantly lower in FH men (54 years) compared to FH women (68 years) (83).

CVD morbidity and mortality in FH has been studied in the UK Simone Broome registry in heterozygous patients with clinical FH diagnosis. In the first publication from 1980-1989 (33), both total CHD and all-cause mortality was found to be significantly higher in the 526 FH patients compared with the general UK population, and highest in age group 20-39 years of age with about a 100-fold increase in CHD mortality, and a nearly 10-fold increase in all-cause mortality. The mortality decreased with age, with no significant excess mortality in patients > 60 years of age. Further, no significant sex differences were reported (33). Furthermore, the prevalence of PVD was investigated. The highest prevalence was found in FH patients 40-59 years of age where the prevalence of intermittent claudication was 8,8% and 9,7% in men and women, respectively (33).

In the second publication from 1980-1995 in 1 185 FH patients covering pre-statin and statins era, median age at registration was 40.3 years in men and 43.9 years in women (84). The excess CHD mortality in young FH patients was verified, and CHD mortality was found to be 48-fold increased in men 20-39 years of age, and 125-fold increased in women (84). In this study the decreasing mortality rate with increasing age was confirmed. During this study

period some patients were started on lipid-lowering therapy, and from January 1, 1992 and onwards 86% of the patients were prescribed statins (84). This study estimated the effects of lipid lowering treatment on mortality rate before and after 1992, and observed a decline in the risk of CHD mortality from a 8-fold increased risk before 1992, to a 3.7 fold increased risk after 1992, by use of statins in FH patients 20-59 years of age (84). Apart from CHD mortality, all-cause mortality, cancer mortality and non-coronary mortality was investigated. Study results showed a non-significant difference in cancer and non-coronary mortality in FH patients compared with the general population. As for all-cause mortality, a higher relative risk was shown in men 20-59 years of age, and in women 40-59 years of age, but no significant differences in total all-cause mortality (84). This study also evaluated the risk of suicides in the FH cohort, of which no increased risk was reported, nor in other deaths from accidents or violence (84). The next publication from the Simon Broome Register investigated the prevalence of diagnosed FH by use of clinical criteria in routine clinical practice in UK, and found that the prevalence of FH was highest in men 50-59 years of age, and in women 60-69 years of age (85).

To investigate the all-cause mortality in first degree relatives of FH patients compared with the general population, two Dutch studies were performed; a family tree study of 855 first degree relatives of 113 index patients (86), and a pedigree study traced back to a single pair of ancestors in the 19th century (38). In the first publication, an increased mortality was found in first degree relatives, and excess mortality occurring in males between age 40-54 years of age, indicating the burden of the untreated disorder occurring among middle-aged males and not influenced by the type of mutation (86). Similar to the Simon Broome study no excess mortality was reported in patients > 80 years of age. In the second pedigree analysis of 250 patients, all-cause mortality was significantly higher in all pedigree members compared with the general population during 1830-1989, even though this varied in the different time periods and generations, indicating an interaction between genetic and environmental factors (38).

In the previous mentioned Japanese study no significant differences was found in mortality due to cerebrovascular disease in FH patients compared with the general population (83). In a UK prospective registry study during 1980-1998 with 2 871 patients in treated heterozygous FH in the Simon Broome Register (87), fatal stroke mortality was investigated before and after the introduction of statins. About 90% of all patients were on statins. Study

results suggested that the risk of fatal stroke was not significantly different in clinical diagnosed statin treated FH patient to that of the general population (87).

In a new publication in the same UK registry and same time period (88), the 2 871 patients were divided into two study groups. One with clinical xanthomatous FH (n=1 569), and one with non-xanthomatous FH (n=1 302). The purpose was to study CHD mortality in these two groups compared with the CHD mortality in the general UK population. The study results showed a similar elevated CHD mortality risk in both patient groups, underlying the importance of equally aggressive treatment with statins in both patients groups (88).

To study the risk factors for CVD as the outcome variable in FH patients, 526 patients were recruited from the Dutch Lipid clinics during 1988-1997 with clinical FH, of which genetically verified in 62% of all cases (89). All study patients received statins. Mean onset of CVD was 46.8 years, and > 37% had a history of CVD. In multivariate analyses, following five risk factors were found to be significantly associated with a high CVD risk in FH patients: male sex, hypertension, age, BMI, low HDL-C (89). To further study the CVD risk factors in Dutch patients with heterozygous FH, a new cohort study with 2 400 patients, of which 95% of all patients were on statins, were recruited from the Dutch Lipid clinics from 1999 in patients > 18 years of age with genetically verified FH (90). In multivariate analyses in this study male sex, hypertension, smoking, diabetes, low HDL-C and high level of Lipoprotein(a) [Lp(a)] were significant independent risk factors for CVD, and explained 17.8% of the variation in occurrence of CVD in FH patients (90).

To determine the CVD event and the mortality in statin treated patients, another Dutch study was performed (91). Unlike the UK study reported from the Simon Broome Register (84), this study divided the 345 FH patients separately into primary and secondary prevention groups, and followed these patient groups during 1988-1997. About 90% of all patients were continuously on statins (91). In total, all-cause mortality was significantly higher in men (1.5-fold increased), but not in women. CVD mortality in patients without previous CVD history was 1.4-fold increased, and mortality from IHD (ICD-9 codes 410-414) was 2.6-fold increased in patients 0-79 years of age compared with the general population adjusted for age and sex. CVD mortality and IHD morbidity was highest in FH individuals 40-59 years of age, 4.3-fold and 7.6-fold increased, respectively with non-significant differences >60 years of age (91). The decreasing mortality rate with increased age was also reported in previous studies (33, 84). In comparison with the UK Simon Broome study, female FH patients had no

increased CVD or IHD mortality risk (91). Other cause mortality was reported to be lower for both sexes in the Dutch study compared with the general population (91).

Mortality has been further studied in UK in the time period 1980-1998 and 1980-2006 in two cohort studies with 2 871 and 3 382 patients 0-79 years of age, respectively with clinical heterozygous FH from the Simon Broome Register (92, 93). In total 54.6% were on statins at study registrations. The patients had clinically diagnosed FH. In the first study CHD mortality was found to 2.5-fold higher in FH patients with no significant differences in all-cause mortality, stroke mortality, and mortality due to accidents and violence. Cancer mortality and non-coronary mortality was found to be significantly lower in FH patients compared with the general population (92). Separately analyses were performed before and after 1992, as statins became available. In the second publication with 3 382 FH patients participating, the mortality analyses showed a 3.4 fold excess CHD mortality before 1992, which was decreased significantly to a 2.1 fold excess CHD mortality after 1992 in patients 20-79 years of age. In the period 1992-2006 the risk of fatal cancer was significantly reduced after the introduction of statins. Although CHD mortality remained elevated despite statin treatment, it was significantly reduced by 37% use of statins, of which CHD was reduced more in women, than in men (93). This study clearly shows the importance of early optimal statin treatment in order to reduce CHD mortality in FH patients.

The efficacy of statins was demonstrated in a Dutch study (94), of which 2 146 patients with clinical FH from the Dutch Lipid clinics without prevalent CVD were followed during 1989-2002 (94). With statin treatment, the risk of CHD in treated FH patients was significantly reduced by 76%, and the risk of MI in patients > 55 years of age was reported to be not significantly different than age matched samples from the general population (94).

A Japanese cohort study including 410 heterozygous clinically diagnosed FH patients from the Japanese lipid clinics investigated the cholesterol-lowering drug ProbucoI in primary and secondary prevention groups on time to first CVD event leading to hospitalization (95). The results showed no significant differences in the primary prevention group (80% on ProbucoI), but a significant difference in favour of ProbucoI in the secondary prevention group (95% on ProbucoI) (95).

To determine the effect of mutation type on premature CVD events, a Spanish cross-sectional study of 811 genotyped patients from the Spanish National FH Register with heterozygous FH >18 years of age was performed (96). Premature CVD was defined as first

CVD event occurring in men < 55 years of age, and in women < 65 years of age. More than 80% were on statins at study inclusion. Mean age at first CVD event was 42.1 years in men, and 50.8 years in women (96). Overall, prevalence of premature CVD was 21.9%. CHD was present in 80% of the first CVD events, of which MI was most frequent in men (57.7%) and angina most frequent in women (50.9%). In patients with premature CVD, 60% of males and 27% of females suffered a second CVD event 1-3 years after the first event (96). Patients carrying null-mutations had significantly higher frequency of premature CVD and recurrence of CVD events (96). Predictors of CVD events were beside mutation type, male sex, smoking (ever), age and total cholesterol (TC)/HDL-C ratio (96).

A Dutch pedigree study with 161 genetically verified FH patients (97), reported that all-cause mortality was 2.5-fold higher when inherited through mother. No significant differences were reported in paternally inherited FH (97).

A Spanish cohort study evaluated the effect of lipid-lowering medications on LDL-C target in 1 852 patients, of which FH was genetically verified in 68% of all patients 20-79 years of age, with a mean age at 45.6 years (98). However, despite 84% were on lipid lowering medications, only 3.4% of patients reached recommended LDL-C values (98). The best predictor for LDL-C goal attainment was the use of combined therapy with statin and ezetimibe adjusted for age, sex, CVD, and CVD risk factors (98).

To investigate the impact of lipid-lowering treatment (predominantly statins) in FH on CVD morbidity and mortality, a South African cohort study recruited 149 homozygous FH patients (128 genetically verified patients) during 1972-2009 (99). From 1990 and onwards all patients received statins, of whom 88% received high dose statins. The use of lipid-lowering therapy was associated with a significant reduction in CVD mortality, and with delayed CVD events in homozygous FH (99).

In a large Dutch FH cohort of 14 283 genotyped heterozygous FH patients during 1994-2013 (100), FH was defined into severe FH (LDL-C >8 mmol/L) and non-severe FH (LDL-C < 8 mmol/L). The main outcome measure was CVD risk. The study results showed a significant increase in CVD risk in severe FH compared to non-severe FH, indicating the importance of a more aggressive LDL-C lowering treatment in these patients (100). However, in this study only 37.7% of all FH patients received lipid lowering therapy.

AIMS OF THE THESIS

The overall aim was to generate new knowledge on mortality and CVD morbidity among all genetically verified FH patients in Norway. Further, to attain knowledge about how cholesterol-lowering therapy affects the prognosis of FH patients in order to improve treatment options.

The specific aims were:

- 1. (Paper I)** To investigate mortality among all genetically verified FH patients compared with the general Norwegian population, based on the main underlying cause of death in relation to age and sex. To investigate causes of death and mean age at time of death. To investigate lipid values in treated deceased FH patients in relation to established treatment guidelines. To evaluate mutation types in deceased FH patients compared with the mutation types in the FH-cohort.
- 2. (Paper II)** To investigate presence of CVD in deceased FH patients at time of death. To obtain information on mean age at time of first CVD event and mean age at time of death in relation to sex differences. To investigate the causes of death, lipid profiles, and use of cholesterol-lowering pharmaceuticals, of statins in particular, and presence of CVD risk factors among diseased FH patients.
- 3. (Paper III)** To investigate incidence and prevalence of different types of CVD in genotyped FH patients leading to hospitalization and to study sex differences. To study mean age at time of first CVD event, leading to hospitalization and re-hospitalization in relation to sex. To study the type of hospitalization. To study whether specific subtypes of CVD is more prevalent in relation to sex. To study CVD comorbidity in hospitalized FH patients. To investigate the awareness of FH in Norwegian somatic hospitals by reporting FH as any diagnosis in discharge records.
- 4. (Paper IV)** To investigate CVD mortality in genotyped FH patients compared with the corresponding general Norwegian population, by including all causes of deaths mentioned any place at the death certificates. Further, to examine the CVD deaths in deceased FH

patients in relation to place and manner. To study the awareness of FH by reporting FH as any diagnosis mentioned at the death certificates.

MATERIAL AND METHODS

Ethics

This work was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK) (case no. 2011/1343) and the Norwegian Data Protection Official at Oslo University Hospital, and complied with Good clinical practice (GCP) and the Helsinki Declaration.

Study design and the patient population

This was a registry-based study of an open FH cohort with up to 22 years of follow-up (1992-2013). All patients in the FH cohort were genotyped and had genetically verified FH. At time of FH diagnosis the patients were included in the UCCG Registry after written informed consent. In paper I the FH cohort consisted of 4 688 patients, of whom 113 deceased patients in the time period from 1992 to 2010. In paper III there were 5 538 patients in the FH cohort, of whom 1411 were hospitalized during 1994-2009. In paper IV the FH cohort consisted of 5 518 patients, of whom 189 deceased patients during 1992-2013. In paper II, 79 deceased FH patients from 1989 to 2010 were included, of whom 60 of the 113 deceased genotyped patients as described in paper I in addition to 19 patients with a clinical diagnosis of FH, of which 9 patients fulfilled the Dutch Lipid Clinic Network criteria for definite FH with a score of eight points or more (15). In the remaining 10 patients a mutation had not been confirmed by the time they died. However, a genetic FH mutation was identified in their living first-degree relatives by investigating their medical records.

The Norwegian Unit for Cardiac and Cardiovascular Genetics (UCCG)

Registry

This PhD project is built around the National patient registry for individuals with genotyped FH in Norway (The UCCG Registry) which is located at the Unit for Cardiac and Cardiovascular Genetics at Oslo University Hospital. This is the world's second-largest of its

kind with full blood samples and medical information for > 6 500 patients with genetically verified FH in Norway. About 1/3 are referred as index patients (patient referred to a genetic test, and FH verified by genotyping) and 2/3 are referred due to cascade screening (relatives of the index patients with FH verified by genotyping). Most Norwegian patients (about 75%) are referred to genotyping by general practitioners (GPs) (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital). The majority of all patients in this registry have heterozygous FH. To date only 12 of the patients in the UCCG Registry have homozygous FH (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital). The UCCG Registry was established in 1998 but it contains information back to 1992 on sex, age, mutation type, height, weight, and lipid values before and after prescribed cholesterol-lowering pharmaceuticals as well as type and dose of pharmaceuticals used at time of genetic testing. It also contains information on clinical stigmata, comorbidity and present CVD risk factors as shown in Table A2 in Appendix, the requisition form to genetic test for FH in Norway.

All persons included in the patient registry must sign a short informed consent. The UCCG Registry identifies the person by the -11-digit personal identification number and it can therefore be linked to other central health registries. Based on a prevalence of 1:200 of heterozygous FH, less than 1/3 of all individuals expected to have FH in Norway are currently diagnosed and included in this registry (15).

The Norwegian Cause of Death Registry (NCoDR)

The Norwegian Cause of Death Registry (NCoDR) has been available since 1951(101). It is mandatory by law in Norway for physicians to complete a death certificate of all reported deaths which are collected by this registry. The death certificates contain information on the underlying death cause and all contributory and immediate death causes (102).

The coding system used in the death certificates is the ICD (101, 103). From 1992 throughout 1995, the 9th revision was used, and from 1996 and onwards the 10th revision was implemented. In international statistics the underlying cause of death is reported (101). By use of ICD codes mortality in different countries can be compared and various causes of death can be followed over time (101, 103). Since 2005, the NCoDR has used the computer program

Automatic Classification of Medical Entities (ACME) developed by US National Center for Health Statistics to identify and secure the correct underlying cause of death according to rules and guidelines established by WHO based on ICD (104).

In 2014 the NCoDR was moved from Statistics Norway (SSB) to the Norwegian Institute of Public Health which is currently the data processor and data controller for the NCoDR. The NCoDR registry contains information on time of death, all causes of death, place, and manner of death in relation to special circumstances. For causes of death the underlying cause of death refers to the disease or injury which initiated the chain of events leading directly to death (102, 103). The immediate cause of death is the final disease/injury/complication which directly caused the death (102). The contributing causes of death refers to other significant conditions contributing to the death, but not directly related to the disease or condition causing it (102). For place of death, in-hospital and out-of-hospital deaths are reported. Out-of-hospital deaths are defined as deaths reported occurring outside a somatic hospital (at home, during transportation or other specified place outside hospital). In-hospital deaths are reported occurring in a somatic hospital. Manner of death is reported for special circumstances defined as deaths due to drug overdose, unknown cause, sudden unexpected death and suicide.

The NCoDR receives annually about 40 000 death certificates and about 3000 autopsy reports and contains medical information on more than 98% of all deaths (102, 105). The NCoDR encompasses all residents, irrespective of whether they die in Norway or abroad, and since 2012 non-residents such as tourists, labor, and migrants who die in Norway are also included (102).

This registry has been validated both internal and externally. In 2011, a Norwegian autopsy study: Diagnostic validity of fatal cerebral strokes and coronary deaths in mortality statistics was published, which showed a substantial agreement between mortality statistics and autopsy findings for both fatal strokes and coronary deaths in the period from 1965 to 2005 in Norway (106).

The Cardiovascular Disease in Norway (CVDNOR)

Cardiovascular diseases in Norway (CVDNOR) is a collaborative project between the University of Bergen and the Norwegian Knowledge Center for Health services (107). All

hospital stays due to a CVD discharge diagnosis were retrieved retrospectively from the Patients Administrative System (PAS) from all Norwegian somatic hospitals from 1994 (the year from which all Norwegian hospitals adopted PAS) throughout 2009 (107). CVDNOR data contains all CVD hospitalizations as main or secondary diagnosis codes (ICD-9/ICD-10) and all CVD related procedure codes (SIF/NCMP/NCSP) performed during the hospital stays (107). Further, CVDNOR data includes age at hospitalization, sex, admissions and discharge dates from different Norwegian hospitals, codes from different departments and wards and transfer dates and information about type of hospitalization such as acute or elective admissions. Apart from all hospitalizations due to a CVD discharge diagnosis, hospitalizations due to pre-eclampsia/eclampsia, congenital heart defects and diabetes mellitus are included.

In CVDNOR an incident AMI is defined as the first AMI event in an individual with no prior hospitalization due to AMI during the previous seven years. A recurrent AMI is defined as a new AMI event occurring >28 days after the first event. If hospitalization for AMI within 28 days of the first event, it is defined as part of the same event (107). An AMI event with PCI is defined as hospitalization due to AMI and PCI procedure code given within 28 days from AMI hospitalization date. An AMI event with CABG is defined as CABG procedure within eight weeks from the AMI event (107). Definition of a hospital stay is according to the 24 hour rule defining a new hospital stay starting more than 24 hours after the previous ended, and if within 24 hours it is classified belonging to the first hospitalization (107).

The main discharge diagnosis is defined as the diagnosis requiring the most resources during a hospital stay. In cases where the same patient was admitted to one hospital ward and later transferred to other wards within the same hospital stay, only the main discharge diagnosis from the first hospital ward is reported. If a patient is re-admitted to the hospital within 24 hours after discharge, this new hospitalization is defined as belonging to the first. If re-admission occurred more than 24 hours after discharge from the first, this is defined as a new hospitalization (107).

During 1994-2009 the definition of AMI in Norway changed. During the 1990s, the WHO criteria formulated in 1979 for AMI was used (108). From 2000, AMI was defined according to the new American College of Cardiology (ACC)/ESC definition (109). In 2007 the Universal Definition of MI was implemented (110).

Registry links and data collection

In paper I and IV the UCCG Registry was linked to the NCoDR. In paper III the UCCG Registry was linked to the CVDNOR database. In paper II patient data on 79 deceased FH patients was collected from medical records at Oslo University hospital, of which 60 of the 79 deceased patients were from the UCCG Registry. The different registry links and data collected are summarized in Tables 5 and 6.

Table 5. Tasks and linkages of the UCCG Registry to NCoDR and CVDNOR

	Tasks:	The UCCG Registry was linked with:
Paper I	Mortality in FH patients 1992-2010	The Cause of Death Registry (NCoDR)
Paper II	CVD morbidity in deceased FH patients 1989-2010	Based on the registry link to NCoDR in paper I (n=60 genotyped FH patients)
Paper III	CVD morbidity Incidence and prevalence of CVD and causes of hospital admissions in FH patients 1994-2009	The CVDNOR database
Paper IV	Mortality in FH patients 1992-2013	The Cause of Death Registry (NCoDR)

Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Table 6. Data collected from the registry links

Registries and database	Responsible for the link	Variables taken
The UCCG Registry		Birth year Time at genetic FH diagnosis Inclusion year in the registry Mutation type Age Sex Lipid profile CVD risk factors Comorbidity
The NCoDR	Statistics Norway (paper I) The Norwegian Institute of Public Health (paper IV)	Time of death <u>Causes of Death</u> -underlying cause of death -contributing causes of death -immediate cause of death <u>Place of death</u> -in hospital death -out of hospital death <u>Manner of death</u> <u>-special circumstances</u>

The CVDNOR	University of Bergen and Statistics Norway (paper III)	Diagnosis (ICD-9/ICD-10) Treatment procedures (SIF-95/NCSP/NCMP) Type of admission (acute/elective) Hospital admission date Hospital discharge date Data on hospitalization Discharge data
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Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Statistical Analyses

The statistical analyses were performed using STATA 13.1, 12-core Parallel Edition, and the Statistical Package of Social Sciences (SPSS Inc, Chicago, IL/ IBM Corp, Armonk, NY, Excel 2010) version 19.0 and 22.0.

Descriptive data were presented as means (standard deviations, SDs) for normal distributed continuous variables, and frequencies (%) for categorical variables. In cases of a skewed distribution, median was reported with 25th and 75th percentile or interquartile range (IQR). Differences in characteristics between groups were tested by independent *t*-test for continuous variables. For comparison of frequencies between categorical variables chi-square test was used or χ^2 test for independence or Fisher's exact two-tail probability test, and the results were presented in number of cases and percentages (%). For skewed distributions, Wilcoxon rank-sum test was used, or Mann–Whitney U test with median and IQR (Q1–Q3). Two-sided P-values <0.05 were considered statistical significant. Age was calculated by subtracting year of birth from calendar year. Age at time of FH diagnosis and inclusion in the UCCG Registry was calculated as year of inclusion minus year of birth. Follow-up time from inclusion in the UCCG Registry was calculated according to calendar year, and year of birth.

The hospitalizations in the FH-cohort (Paper III) were described based on data extracted from the CVDNOR database according to sex, birth year and year of hospitalizations. Hospital re-admission in the FH cohort was defined as more than one hospital stay. Age at hospitalization was calculated by subtracting year of birth from year of hospitalization. As repeated hospitalizations of the same individual led to dependence between observations of hospitalization, we applied repeated measures logistic regression to test for sex differences. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were reported. A Wald test was applied to study interaction between age and sex in the analysis of CVD hospitalizations.

In Paper I and IV the mortality in the UCCG Registry was compared with the mortality in the general Norwegian population according to sex, birth year and calendar year. All estimations were based on the following criteria: From time of patient inclusion in the UCCG Registry and the FH cohort to the time point the patient reached the study endpoint which was defined as year of death or end of study. Age at death was calculated as year of death minus year of birth and calculated in whole numbers without decimal notations at the end of the actual year of death.

The results were reported as standardized mortality ratios (SMRs) with corresponding 95% CIs. SMRs were calculated by indirect standardization, and derived from the ratio of the number of observed deaths (D_p) to the number of expected deaths (E_p) in the patient population: ($SMR = D_p / E_p$) (111, 112). In paper I the 95% CIs for SMR were calculated as: $(e^{-1.96/\sqrt{D_p}} \cdot SMR, e^{1.96/\sqrt{D_p}} \cdot SMR)$ (112, 113), and in paper IV upper and lower confidence limits (CL) were obtained using the normal approximation to the Poisson distribution using the following formula: $CL = e^{\pm 1.96/\sqrt{D}} \cdot SMR$, where D denoted the number of observed deaths in the patient population. In paper I the number of expected deaths in the patient population (E_p) was estimated by use of the below formula. All calculations were based on equal mortality as in the general Norwegian population and were estimated by summing up total time spent in the cohort (in the patient population) for every birth and calendar year and multiplied with the mortality rate for men and women in the general Norwegian population for all corresponding x and y values: $E_p = \sum_{y=1992}^{2010} \sum_{x=1913}^{2010} M_p(x, y) \cdot R(x, y)$ (111, 113). Total time spent by the patient population during the calendar year (y) for patients born in year (x) was given as: $M_p(x, y)$. The mean population in the year y for population born in year x was given as: $M(x, y) = \frac{1}{2} (L(x, y) + L(x, y+1))$, where $L(x, y)$ defined the Norwegian population per January 1st year y born in year (x). The mortality rate in the Norwegian population born in year x in year y was given as: $R(x, y) = D(x, y) / M(x, y)$, where $D(x, y)$ was defined as the number of observed deaths in the Norwegian population born in year (x) in year (y) (111, 113).

In paper IV data was obtained from the NCoDR both for the patients in the UCCG Registry and for the total population in Norway in order to calculate reference rates for

calculation of the SMRs. The mid-year population for a specific calendar year was calculated as the mean of the population January 1st the current year and January 1st the year after, stratified on year of birth and sex. Birth year- and calendar-year-specific mortality rates for men and women in the total Norwegian population were calculated using counts of deaths from specific causes from the NCoDR as nominator and the mid-year population as the denominator.

The expected number of deaths for men and women were calculated separately for each combination of birth year (x) and calendar year (y) in the UCCG Registry as time spent in the cohort multiplied by the mortality rate for the same combination of birth year and calendar year in the total Norwegian population. The total expected number of deaths for men and women in the patient population was calculated by the following formula:

$$E_p = \sum_{y=1992}^{2013} \sum_{x=1913}^{2013} T_p(x, y) \cdot R(x, y)$$

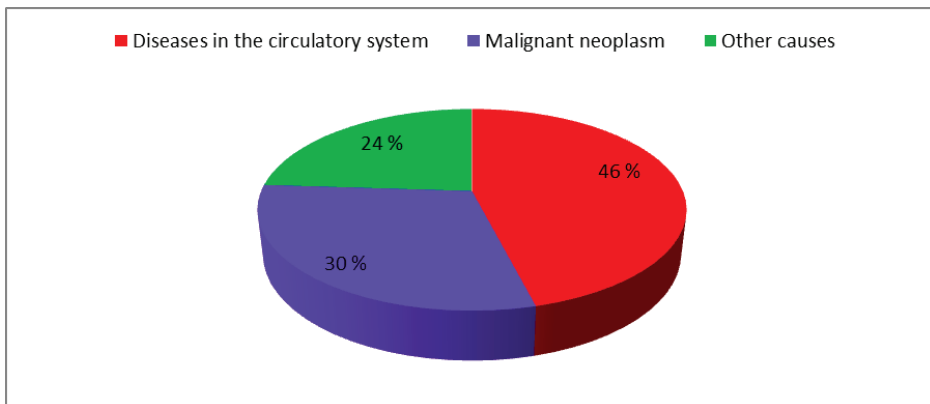
where T_p denoted time spent in the patient cohort for a specific combination of birth year (x) and calendar year (y). R denoted the corresponding mortality rate in the total Norwegian population for the same combination of birth year and calendar year.

SUMMARY OF RESULTS

Paper I

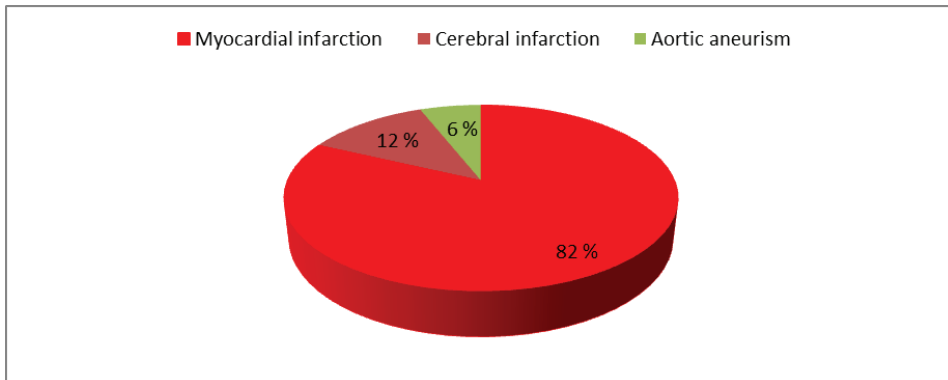
In this registry-based study, 4 688 male and female patients from the UCCG Registry with verified molecular genetic diagnosis of FH in the period from 1992 to 2010 were linked to the NCoDR. During this time period there were 113 observed deaths. Mean age at time of death was 61.1 years. CVD was the most common cause of death (46.0%), followed by cancer (30.1%) as shown in Figure 10. Of the CVD deaths, MI was most frequent (Figure 11). Compared with the Norwegian population, CVD mortality based on the underlying cause of death, was significantly higher in the UCCG Registry in all age groups below 70 years: SMR= 2.29, 95% CI (1.65-3.19) both sexes included, SMR= 2.00 (1.32-3.04) in men, and SMR= 3.03 (1.76-5.21) in women. The risk for death of CVD was 8-fold increased in FH patients younger than 40 years of age. Overall, no significant differences were found in all-cause mortality or cancer mortality. The FH patients were about 15-21 years younger at time of CVD death compared with the corresponding general Norwegian population.

Figure 10. Causes of deaths in the 113 deceased patients from 1992 to 2010



Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Figure 11. Causes of CVD deaths among the 113 observed deaths from 1992 to 2010



Source: Liv J Mundal, the Lipid Clinic, Oslo University Hospital

Paper II

In this study presence of CVD, lipid profile, and use of cholesterol-lowering pharmaceuticals and cause of death was characterized in 79 deceased Norwegian FH patients of whom we had access to medical records from 1989 to 2010. Mean age at first CVD event was 44 years. Mean age at time of death was 60 years. CVD was the cause of 50% of the deaths. At time of death, 93% of the FH patients had established CVD and 69% had experienced one or more MIs. The FH patients were divided into two groups (cut-off 60 years); FH patients who died at a younger age (mean age 51 years) and at an older age (mean age 71 years). More of the younger FH patients received statins (98% versus 81%, $p=0.038$), and fewer received niacin (0% versus 17%, $p=0.019$) compared to the older patients. The last measured LDL-C level was higher in the younger compared to the older FH patients (5.3 versus 4.4 mmol/L, $p=0.033$). There were more current smokers among the younger FH patients compared to the older patients (55% versus 10%, $p=0.001$). Importantly, there were no sex differences in age at first CVD event or age at time of death.

Paper III

In this registry study data on 5 538 patients with verified genotyped FH were linked to data on all Norwegian CVD hospitalizations, and hospitalizations due to pre-eclampsia/eclampsia, congenital heart defects and diabetes. During 1994-2009 a total of 1 411 FH patients were

hospitalized. CHD, ACS or AMI was reported in 90% of all hospitalized FH patients. Mean (SD) age at first hospitalization and first re-hospitalization was 45.1 (16.5) and 47.6 (16.3) years, respectively, with no significant sex differences ($p=0.66$ and $p=0.93$, respectively). Hospitalization was more frequent among FH men (26.9%) than FH women (24.1%) ($p=0.02$). Median (25th-75th percentile) number of hospital admissions was 4 (2-7) per FH patient, with no significant sex differences ($p=0.87$). Despite previously known genetically verified FH at time of hospital admission, the FH diagnosis was registered in only 45.7% of the patients at discharge.

Paper IV

In this study the UCCG Registry consisting of 5 518 patients with genotyped FH was linked to the NCoDR. During 1992-2013 there were in total 189 observed deaths of which CVD was the most common cause (42.3%), followed by cancer (29.6%). Mean age at CVD death was 64.5 years (range 33-91). CVD mortality, including all CVD deaths mentioned any place on the death certificate, was significantly higher in FH patients compared with the general Norwegian population < 70 years of age and highest in age group 20-39 years: SMR 4.12, 95% CI (1.85-9.18) decreasing to SMR 0.77, 95% CI (0.50-1.19) for those > 80 years. As for place of death, total CVD deaths occurring out-of-hospital were significantly higher in age groups 0-69 years and highest in those 20-39 years of age: SMR 12.35, 95% CI (5.14-29.70) compared with the corresponding general Norwegian population. At time of death FH was registered as any contributory death cause in only 3.2% of all death certificates.

Discussion

Mortality in genotyped FH patients (Paper I)

In paper I the mortality in the FH-cohort, consisting of 4 688 genotyped FH patients from the UCCG Registry, was compared with the mortality in the corresponding general Norwegian population from 1992 to 2010 (114). During this time period there were overall no significant differences in all-cause mortality or in cancer mortality in FH patients compared with the general Norwegian population. Total mean age at time of death was 61.1 years. The majority of the patients were on statins (88%), and many had used statins for >20 years.

Mortality in FH has previously been studied in the UK Simon Broome Register where a decrease in all-cause mortality and cancer mortality were reported (92, 93). Most epidemiological data suggest that long term lipid lowering treatment with statins is not associated with the development of cancer, although data on several years of exposure to statins are still incomplete (115-118). In the present study 30% died of cancer, while in Norway cancer was responsible for 35% of all deaths in 2010 (119), suggesting that long-term use of statins did not increase the risk for death of cancer. In the UK Simon Broome Register statin therapy showed no adverse effect on rates of cancer incidence or non-cardiovascular mortality for either sex (93). After the introduction of statins, cancer mortality was significantly lowered compared with the general population (93). In statin treated patients without known CHD all-cause mortality was 33% lower than in the general population, mainly due to a 37% lower risk of fatal cancer (93).

The main finding in this present study was the significantly higher CVD mortality in genotyped FH patients compared with the general population where CVD mortality based on the underlying cause of death was significantly higher in all patients in all age groups below 70 years despite available cholesterol lowering pharmaceuticals (114). CVD mortality was highest in young FH patients 20-29 years of age where the risk for CVD death was 8-fold increased, to that of the general population over 70 years of age (114). Decreasing CVD mortality by age has previously been reported in other FH registries such as in the UK Simon Broome Register. In a publication from 1991 in the pre-statin era mortality from CHD was increased approximately 100-fold in young adults aged 20-39 years, and 4-fold in patients 40-59 years (33). The mortality decreased with age with no significant excess mortality in patients > 60 years of age. Further no significant sex differences were reported (33). In a UK

publication from 1999 the excess CHD mortality in young FH patients was verified, and CHD mortality was found to be 48-fold increased in men 20-39 years of age, and 125-fold increased in women (84). In this study the decreasing mortality rate with increasing age was confirmed (84). This study estimated the effects of lipid lowering treatment on mortality rate before and after 1992, and observed a decline in the risk of CHD mortality from a 8-fold increased risk before 1992, to a 3.7 fold increased risk after 1992 by use of statins in FH patients 20-59 years of age (84). After the introduction of statins, CHD mortality decreased to about 2-fold fold excess CHD mortality in patients 20-79 years of age compared with the general UK population (93). Although CHD mortality remained elevated despite statin treatment, it was significantly reduced by use of statins (93) which clearly emphasized the importance of early cholesterol-lowering treatment in order to reduce premature CHD mortality in FH patients. To determine the CVD event and the mortality in statin treated patients, a Dutch study was performed, of which about 90% of all patients were continuously on statins (91). In total, all-cause mortality was significantly higher in men (1.5-fold increased), but not in women. CVD mortality in patients without previous CVD history was 1.4-fold increased, and mortality from IHD was 2.6-fold increased in patients 0-79 years of age compared with the general population adjusted for age and sex. CVD mortality and IHD morbidity was highest in FH individuals 40-59 years of age, 4.3-fold and 7.6-fold increased, respectively with non-significant differences >60 years of age (91). It seems that the relative risk of CAD in FH patients > 60 years of age is not significantly higher than in the general population, as compared with a high risk at a younger age possibly reflecting stabilization of coronary lesions by lipid-lowering therapy (93, 94). Patients who survive through middle age no longer appear to be at substantially increased risk of CAD (94). However, in the present study only patients > 70 years of age are of similar CVD risk as in the general population.

Importantly, the results from the different studies are not totally comparable as a clinical criteria of FH was used in the UK studies and not strict molecular genetic tests, hence some patients may have been misclassified. Further, the UK studies reported separate results only for specific sub diagnoses of CVD as opposed to this present study which included all in the mortality analysis. Furthermore, our study is larger, and all patients had genetically verified FH.

In the present mortality study no FH patients died of CVD younger than 20 years. Those who died were older at time of diagnosis (mean age 54.8 years) compared to all FH

patients in the UCCG Registry (mean age 33.6 years), and had a shorter mean follow-up time on lipid-lowering medications from time of FH diagnosis (6.3 years versus 8.0 years). Patients diagnosed late in life had thus been exposed to high LDL-C levels for many years with an increased risk of atherosclerosis, and some FH patients may have died due to CVD before being diagnosed. As shown in Figure 10, CVD was responsible for 46% of all deaths in the FH-cohort, while in the Norwegian population CVD was responsible for 37% of all deaths (119).

The deceased patients had the same four most frequent mutation types as found in the FH-cohort (120), suggesting that type of mutation was not important for the risk of CVD death.

Evidently, the prognosis from CVD has improved in FH patients due to statins but not to the same level as in the general population which may be explained by several factors. Although the majority were on statins, and it is commonly accepted that lowering of LDL-C reduces the risk for CVD (121, 122), the deceased FH patients did not reach recommended treatment targets for LDL-C (15, 39, 114). It is a fact that approximately 50% of patients with chronic diseases do not take medications as prescribed due to various reasons (123). In the Copenhagen General Population Study only 48% of the FH patients received statins (2). In the present study some patients did not receive statins due to end-stage cancer. Further, late upstart of lipid lowering treatment due to high age at time of diagnosis apart from inadequate treatment implied already existing severe atherosclerosis and a significantly higher CVD risk. Even though statins may normalize LDL-C levels, it seems that there is an inflammatory response in statin-treated FH patients which may be due to many years of exposure to atherosclerosis before statin therapy is initiated (124).

FH patients had a significantly lower other-cause mortality compared with the Norwegian population. Similarly, in UK Simon Broome Register non-coronary mortality was found to be significantly lower in heterozygous FH patients compared with the general population (92, 93). This may partly be due to patients being more motivated for a healthy life style and regular health checks, once diagnosed with FH. However, we cannot exclude other explanations.

Presence of cardiovascular disease at time of death (Paper II)

In paper II the prevalence of CVD at time of death was studied from 1989 to 2010 in 79 deceased FH patients, of whom 60 patients had genetically verified FH, and 19 patients had a clinical FH diagnosis (125). Based on the results in paper I, where CVD accounted for 46% of all deaths based on the main underlying cause of death, we wanted to explore the presence of CVD in deceased FH patients by investigating their medical records. The main finding was that 93% of the deceased FH patients had established CVD at time of death, and 69% had experienced one or more MIs. However, CVD was reported as the underlying cause of death in the death certificates in only 50% of the FH patients which is similar to the results in paper I. In the present study the majority had experienced one or more CVD events before statins were initiated, which suggested that the deceased patients were diagnosed with FH after the first CVD event occurred, underscoring the severity of a late FH diagnosis (15).

Importantly, there were no sex differences in mean age at the first CVD event (44 years) or in mean age at the time of death (60 years), which is a new and important finding (125). Previous studies in the general population have reported a 10-year difference in CVD risk in favor of women (42). Even though the prevalence of CVD deaths in the FH patients was not very different from the general population, the FH patients had a significantly lower mean age at time of CVD death, in accordance with our results in paper I (114).

A previous cohort study (n=2 146 patients) observed a 76% overall risk reduction in CHD in statin treated FH patients during a mean follow-up of 8.5 years (94) where statins were shown to lower the risk of MI in FH patients to the same level as the general population (94). This result is not in accordance with our results in the present study or in the mortality study presented in paper I even though both studies were carried out in the “statin era”. Despite statin treatment, CVD mortality was still significantly higher in the FH cohort (paper I), and age at time of death was lower in deceased FH patients than in the general population (paper I and II). Many patients died young after having experienced one or more premature CVD events such as MI. In the UK Simon Broome studies a reduction in CHD mortality by use of statins was reported, but not to the same level as in the general population (33, 84).

The deceased patients were divided into two groups (cut-off 60 years); FH patients who died at a younger age (mean age 51 years) and at an older age (mean age 71 years). Although more of the younger FH patients < 60 years of age received statins (98%) compared

to the older patients (81%), their last measured LDL-C level was higher compared with older FH patients (5.3 vs. 4.4 mmol/L). This emphasises the importance of optimal follow-up of young FH patients to secure a good compliance on pharmaceuticals, and to optimize the treatment once given to reach recommended treatment targets (15). The FH patients in this study received statins for an average of eight years prior to death. However, only 54% of the FH patients, with a highly premature mean age of 44 years at first CVD event, received a potent type of statins. Inadequate dose and late initiation of statins probably lead to a higher risk of CVD deaths.

It has been estimated that before the age of 65 years, approximately 50% of women and 85% of men with FH have experienced a coronary event if not appropriately treated (5). The present study suggests that the numbers are even higher since 80% of the women and 90% of the men who died had established CHD at time of death. In women long term exposure to high LDL-C from birth and late FH diagnosis may be so detrimental that it counterbalances the positive effect of sex on CVD. Further, pregnancy and lactation leads to the disadvantage of fewer effective years of treatment in women. The present data underscores the importance of treating both sexes equally efficient in FH as statins are of similar effectiveness in prevention of CVD in men and women with equivalent CVD risk (42).

As for clinical manifestations of FH, xanthelasmas, xanthomas, or corneal arcus were present in 31%, 57% and 62%, respectively of the deceased patients. In paper I the presence of xanthelasmas and xanthomas were lower; 16% and 42% respectively, but the information on clinical signs were only available in 88 of the 113 observed deaths. No significant differences concerning presence of clinical signs and mean age at time of death was reported (114).

Smoking as a CVD risk factor was more prevalent in the young deceased FH patients compared with the older patients (55% versus 10%) which is consistent with previous findings (90, 126), and stresses the importance of early and optimal follow-up of young FH patients as smoking is a major risk factor significantly associated with CAD (125, 126).

Apart from smoking, diabetes was more prevalent in the deceased FH patients (22%) and much higher than expected in corresponding general population, seemingly representing a major CVD risk factor for death in FH patients. Further, the prevalence of atrial fibrillation among the FH patients was high and approximately at the same level in deceased patients

aged 60 years as in those aged 85 years or older (17.8%) in the general population (127), reflecting the massive burden of CVD in the FH population.

Furthermore 15% of the deceased FH patients in our study had aortic aneurysm compared to 2.2% in women and 8.9% in men in the general Norwegian population (128). In the general population aortic aneurysm is two to six times more prevalent in males than in females (128). No such sex differences were reported in this present study. As for surgical procedures 29% of the deceased FH patients had experienced one or more CABGs. The high number of CABGs underscores the severity of FH, but must also be considered in context to the time of which the data were collected.

The present study clearly emphasises the severity of FH and the urgent need for early diagnosis and treatment in FH patients to prevent the high premature CVD morbidity and mortality equally in FH men and FH women. The majority of deceased FH patients suffered from CVD at time of death even though the underlying cause of death was due to a non-CVD condition in 50% of all cases.

Cardiovascular disease morbidity in FH patients (Paper III)

In paper III CVD morbidity in FH patients leading to hospitalizations during 1994-2009 was reported. The results showed that both FH men and FH women, despite prescribed lipid lowering pharmaceuticals, had a lower mean age at time of first hospitalization (mean age 45.1 years) compared with the general Norwegian population (mean age 64.9 years). Further, no significant sex differences in age at time of first hospitalization in the FH patients was reported compared with the general Norwegian population where men had a lower mean age (64.0 years) than women (66.0 years) (107). This is in accordance with the study results in paper II, where no sex differences in mean age at time of first CVD event or in mean age at time of death were reported, which may be explained by FH women being significantly older at time of FH diagnosis compared to FH men indicating a later upstart on statins in women. Similarly, in a Spanish study of (n=811) genotyped FH patients a highly premature mean age at time of first time CVD event was reported but at a different mean age in relation to sex (42.1 years in men and 50.8 years in women) (96).

About 90% of all CVD hospitalizations were due to IHD. In the Spanish study CHD was present in 80% of the first CVD events, of which MI was most frequent in men (57.7%) and angina most frequent in women (50.9%) (96). In the present study hospitalizations due to IHD were significantly higher in men than in women in addition to hospitalizations due to heart failure, atrial fibrillation and aortic aneurysms. No sex differences were reported in hospitalizations due to cerebrovascular disease, total stroke, hypertension, aortic stenosis or diabetes. As for sex differences in selected comorbidities reported during hospital stays the same results were seen. The results for aortic aneurysms differed from the results reported in paper II in deceased FH patients where no such sex differences were found. Nor did we find significant differences in the CVD sub diagnoses in deceased patients in the previous work.

The hospitalized FH patients were significantly older (mean age 47.6 years) at time of diagnosis and inclusion in the UCCG Registry compared to FH patients who had not been hospitalized (mean age 29.2 years). A late initiation of statins implied many more years with untreated atherosclerosis before being diagnosed thus increasing the total life-long cholesterol burden.

About 25% of all individuals with FH were hospitalized due to CVD, and the hospitalizations were more frequent among FH men than FH women, of which the majority of CVD hospitalizations in both sexes were in the age group 40-59 years. The sex differences were smaller in FH patients ≥ 70 years of age. However, there were no sex differences in median number of hospitalizations in the FH-cohort which seemed to be higher than in the Norwegian population (68).

Although re-hospitalizations due to CVD are common, accounting for about 29% of all cases in Europe (129), it was even more frequent in the FH population of which 80% of all patients had one or more hospital re-admission about 2.5 years after the first admission. These data are in accordance with the results in paper II demonstrating that about 70% of FH patients had experienced one or more MIs at time of death (125). In the previously mentioned Spanish study of genotyped FH patients with premature CVD, 60% of males and 27% of females suffered a second CVD event 1-3 years after the first event (96). Importantly, we found no significant sex differences in mean age at time of re-hospitalization in the FH-cohort (47.6 years). The high number of re-admissions in the FH-cohort underscores the importance of early follow-up and early interventions in FH patients.

Whereas most hospitalizations in Norway are acute admissions (68%) (68), elective hospitalizations dominated (60.6%) among the FH patients. Elective re-admissions are usually due to scheduled coronary angiography, PCI or cardiac surgery (130). However, in the FH cohort we found no differences in the use of CVD diagnostic invasive procedures and treatment in the hospitalized FH patients compared with the Norwegian population that could be related to the high numbers of elective hospitalizations and re-admissions (107). The high numbers of elective admissions may partly be explained by hospitalized FH patients being younger at time of first hospitalization compared with the corresponding general population. Once established CVD in young age, higher re-admission rates are expected (129). In Norway the number of patients who underwent PCI and CABG increased significantly from 2001 to 2009 in all age groups (131). Norwegian men had significantly higher frequencies of PCI and CABG compared to women (131). In the present study FH men had significantly more hospitalizations with PCI compared to FH women, but there were no significant sex differences in hospitalizations due to CABG and coronary angiography which suggests that CVD risk differed less between FH women and FH men than found in the general population (107). The lack of sex difference in prevalence of CVD events was also observed in a recent study among deceased FH patients, further supporting such notion (125). In paper II we reported that 29% of the deceased FH patients had experienced one or more CABGs prior to death which underscores the severity of FH.

Furthermore, the overall few numbers of diagnostic and invasive treatment procedures reflect the time period this study covered. In Norway declines in rates of MI was observed in the time period studied (132, 133), thus lower rates of coronary revascularization (declined by 40% from 2003-2012), with most rapid declines in elective PCI and CABG (133). Apart from the use of invasive procedures /revascularizations, predictors of re-admissions varies (130), according to age, sex, comorbidity, and complications like arrhythmias, bleedings, and re-infarctions (134). Efforts to reduce re-admissions should be targeted to patient groups at risk (134), such as the FH patients.

The fact that many FH patients did not reach target lipid values had an important impact on the CVD risk. Many of the FH patients started on lipid lowering treatment at a too high age due to late diagnosis and were exposed to high LDL-C levels for many years (114). Statin adherence is associated with reduction in CVD related hospitalizations and thus subsequent health care costs (135).

The awareness of FH was low in the Norwegian hospitals, of which less than 50% of all hospitalized patients with a previously known genetic FH diagnosis had FH registered as any diagnosis at discharge. This finding is important as it implies either patient's unawareness of reporting FH at hospital admission, or physicians' ignorance of FH, hence not asking the patient. Moreover, significantly fewer FH women than men were registered with FH at discharge. The main issue seems to be unawareness of FH among physicians working at hospitals. In hospitalized patients the FH diagnosis is severely under-reported (81) even though FH is a major contributing factor to premature CVD events and FH patients annually account for 5% of all MIs in patients < 60 years of age (80). Better identification of the FH patients during hospital stay, especially young FH patients admitted to Departments of Cardiology, is important as these patients should be referred to lipid clinics at discharge (81). The majority of FH patients are referred to genotyping from GPs (62%), compared to cardiologists (16%) and internists (6%) (90). In Norway even higher numbers (about 75%) are referred to genotyping by GPs (personal communication, Trond P. Leren, MD, Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital). In an audit of 334 FH patients with premature CAD admitted to a Department of Cardiology (136), FH was frequently not considered in adult patients among specialists in a public hospital, and in half of the medical records reviewed it was not possible to evaluate the presence of FH owing to a lack of key information (136). Further, FH is under-recognized in cardiology practice (137). A recent survey of cardiologists performed by the American College of Cardiology reported a need for greater awareness of FH among cardiologists (137). Given the fact that many patients with FH may first present to specialists at time of a major coronary event, it is important that cardiologists have pre-existing strategies to manage these high-risk patients and consult a lipid specialist (137). FH may easily be overlooked in the busy turnover at hospitals where the main focus is on the invasive strategy of the acute event, rapid and early patient discharge. Furthermore, as no specific diagnostic ICD-10 code exists for FH, it makes it even more difficult for physicians to report this diagnosis in hospital records at discharge.

The present study illustrates the high CVD morbidity among FH patients resulting in high numbers of hospitalizations and re-hospitalizations at an equally mean age in both sexes. Although FH patients have frequent hospital admissions due to CVD, the awareness of FH as an important contributing factor to CVD is disturbingly low, reported in less than 50% of all discharge records.

Cardiovascular disease mortality and place and manner of deaths in FH patients (Paper IV)

In paper IV the main approach was to report CVD mortality in the FH-cohort during 1992-2013 based on all causes of deaths compared with the general Norwegian population. In the previous papers (paper I and paper II) only the underlying cause of death was reported. It came to our attention by examining the medical records of the deceased FH patients in paper II that the majority of the patients suffered from CVD at time of death even though the underlying cause of death was due to a non-CVD condition and CVD was only reported as the cause of death in 50% of all cases. In order to secure the highest possible reliability of the study results we included all causes of CVD deaths in the analyses in paper IV by investigating the underlying, all immediate and contributory causes of CVD deaths mentioned in the death certificates in deceased FH patients in the mortality analyses. Further we studied place and manner of deaths in FH patients.

The CVD mortality including all causes of deaths was found to be significantly higher in FH patients in all age groups < 70 years compared with the general Norwegian population. Further the CVD mortality was highest in the young age group (20-39 years) and decreased with age to that of the general population in patients > 70 years of age. Similar results for CVD deaths based only on the main underlying death cause were reported in paper I (114). As in the UK Simon Broome mortality studies (33, 84) this present study did not contain separate primary and secondary prevention groups as described in the Dutch mortality study by Mohrcladt et al (91). However, in these studies the FH patients were only clinically diagnosed, and some patients may have been misclassified. In the present study all patients had a genetically verified FH diagnosis. Further, in the UK study only CHD mortality was accounted for, not total CVD mortality as in the Dutch study and in our study. Further, the number of patients were considerably smaller in the Dutch study (n=345) (91) and the UK study (n=1 185) (84) compared with the present mortality study (n= 5 518) and in the mortality study presented in paper I (n= 4 688) (114).

As reported in paper I and II the mean age at time of CVD death was low in the FH-cohort, which represents a more than 15 years shorter life span for both sexes compared with the general Norwegian population (114, 138), which underscores the vital importance for this

patient group to be diagnosed and treated to target lipid values as early as possible in order to prevent these premature CVD deaths.

The most important finding in the present study was the high number of CVD deaths occurring out-of-hospital in all FH patients 20-69 years of age compared with the corresponding Norwegian population. In individuals with FH younger than 40 years of age the risk for out-of-hospital CVD death was >12-fold increased compared with the general Norwegian population. Among FH women 20-39 years of age the risk of out-of-hospital CVD deaths was >19-fold increased. The fact that the majority of young FH patients died out-of-hospital CVD deaths indicates huge unawareness of the CVD morbidity in these young patients. For all-cause mortality in relation to place of death we found no such differences. Premature events which appears in patients < 40 years of age, can be pathognomonic with FH (1). As FH is a common genetic disorder which leads to premature CHD and sudden cardiac death (SCD), some of the premature CVD deaths occurring out-of-hospital in young FH patients may have been related to SCD, as sudden death and MI are principal causes of deaths in FH patients (33). As earlier reported in the Danish and the Japanese study in FH patients, 16.1% and 22% of all death causes respectively were due to sudden deaths (82, 83). In another Danish study the LDL-receptor gene and the ligand-binding region of the APOB gene were screened in 52 cases by postmortem blood samples from autopsies of SCD in patients < 40 years of age suspected of having FH based on autopsy findings of atherosclerosis in the coronary arteries (139). This study group consisted of 41 men and 11 women with coronary atherosclerosis. In this SCD cohort, 7.7% had a rare sequence variant in the LDL-receptor gene, of which 5.7% were suspected to be pathogenic mutations (139). In Norway during 1990-1997 MI was reported to be the most common cause of sudden deaths in sports based on autopsy reports in young patients aged 15-34 years, of which the coronary deaths occurred at a mean age of 30 years (140). Furthermore, many young patients had advanced coronary disease at time of death (140).

As for manner of death, there were no significant differences in special circumstances in the FH cohort compared with the general Norwegian population in the present study. One might speculate that the three sudden unexpected deaths could have been related to CVD and thus would have led to even higher CVD mortality than reported.

Further, we found no significant differences in suicides or in excess deaths due to violence or accidents in the FH cohort compared with the general population, which is in accordance with previously results reported in the UK Simon Broome studies (84, 92).

No genotyped FH patients younger than 20 years died of CVD. Those who died were on average diagnosed late in life, and were about 23 years older at genotyping compared to the survivors, underscoring the importance of earliest possible FH diagnosis.

Furthermore, unawareness of FH and the extent of CVD morbidity in young FH patients were demonstrated by the fact that most death certificates did not include FH as any contributory cause of death despite the FH genotype being known before the time of death.

Strengths and limitations

All Norwegians have a unique identification number allowing for linking data across nationwide health registries. An important strength in this study was the high number of genotyped FH patients and the complete follow-up.

Few, if any, other studies have investigated the mortality and CVD morbidity in such a high number of genotyped FH patients. However, less than 1/3 of the estimated numbers of Norwegian individuals expected to have FH are genotyped, although the genotyping is easy to perform. The present study may therefore have underestimated the CVD mortality and morbidity in the FH population. The mortality rates and hospitalization rates might have been different as many with undiagnosed FH are not accounted for. As the mean age was about 33.7 years at time of genetically verified diagnosis and inclusion in the UCCG Registry, some severely affected FH patients may have died young out-of-hospitals before being diagnosed, and some may not have been hospitalized for different reasons such as less severe forms of CVD misdiagnosed as other disorders.

Further, this study did not take into consideration change of ID-number or emigration to other countries, but this would not have changed the main findings in our study since only a minority of the patients (0.4%) was lost to follow-up.

Although it may seem that FH patients have about 15-21 years lower mean age of CVD deaths compared with the Norwegian population (114), these two populations were not totally comparable as the mean age in the FH cohort was slightly younger (about 4.3 to 4.8

years) than in the Norwegian population in the same time period (114). Ideally, when comparing the mean age at time of death in two different cohorts, the exact mean age in the two populations at study inclusion should have been present. With equal mortality rates one would expect a lower mean death age in a younger population and vice versa. However, the registry links gave corresponding data from the Norwegian population from the exact same time period.

In public statistics only the underlying cause of death is reported (102). In this thesis we provided a complete report on all causes of death by the registry link to the NCoDR which gave information on all causes of death by including underlying, all contributory and immediate causes of deaths in all deceased patients the FH-cohort compared with the general Norwegian population. Some few inaccuracies in the ICD-10 codes made it difficult to establish the exact cause of death as two FH patients had diabetes mellitus as the underlying cause of death. As diabetes mellitus is associated with up to four times increased risk of CVD, it is likely that these two persons died of CVD, but it is impossible to be absolute certain. Seven FH patients had pure hypercholesterolemia as the underlying cause of death, and were most likely to suffer from CVD deaths.

The registry link to the CVDNOR gave data on CVD morbidity in hospitalized patients. A present strength in this study was that complete data on all somatic CVD hospitalizations in the entire Norwegian population during 1994-2009 were included. However, some of the confounding factors that could influence on mortality, CVD morbidity and hospitalization frequencies were not accounted for. The CVDNOR did not provide information on smoking habits, dietary habits, BMI, pharmaceuticals, or data on physician follow-ups or participation in CVD rehabilitation programs (141). Nor were there available data on MI subtypes before implementing the ICD-10 codes which is important as there are different treatment guidelines.

The majority of the blood samples were analyzed by the Department of Medical Biochemistry at Oslo University Hospital. A few of the baseline lipid blood samples were taken by the referral doctors and analyzed at local laboratories. Analyses of blood samples from different laboratories may to a lesser extent have influenced the results. The latest treatment lipid values were chosen and mean values calculated. However, the absence of

detailed data on lipids in this study limited the ability to evaluate factors associated with living longer with FH.

Some care, however, is needed in interpreting our findings. The deceased patients were not a random sample of the total Norwegian FH population as many patients were followed up at the Lipid Clinic with an experienced staff. Reflecting the time frame the collected data from the medical records represents, all values were not available for all FH patients. For the same reason, detailed information on presence of CVD such as different types of MIs was scarce and we did not have available information on coronary revascularisation procedures in the medical records such as information on PCI in paper II. Further, not all medical records for the deceased FH patients were available. In paper I and II clinical information was extracted from medical records in 60 of the 113 deceased FH patients.

Although there are reasons to believe that the FH patients enrolled in the National UCCG Registry are representative for the entire Norwegian FH population, we cannot exclude any selection bias in this FH cohort. There might be a potential bias at the level of physician as some physicians may have more knowledge on FH thus be more eager to refer individuals to genotyping than others. The majority of patients are referred to genotyping by GPs (90). However, most patients were genotyped because a family member had been diagnosed with FH, not that the index patients had severe FH (25). There is no reason to expect that only the most severe cases were genotyped as most Norwegian patients are referred to genotyping due to cascade screening (relatives of the index patients with FH verified by genotyping). The wide age range within the FH cohort indicates its representativeness as such. Furthermore, genetic testing is free of charge and all physicians in Norway can order it. In the registry links neither to the NCoDR selection biases was not an issue, nor for data on hospitalizations due to CVD as all somatic CVD hospitalizations from the entire Norwegian population during 1994-2009 were included were potential selection biases minimized.

Our study was mainly limited to a Caucasian population where 92.4% of the patients in the FH cohort were native Norwegians (142). It is therefore important to compare these results with similar studies from different countries and other ethnicities.

The importance of FH registries

National FH registries are key instruments for providing new knowledge on FH. Complete registries are important for research by registry link to other national health registries and as a tool for health economic evaluations. Further, the purpose of FH registries is to secure more FH patients being diagnosed in order to achieve earliest possible preventive treatment and clinical follow-up (143). By use of FH registries data on morbidity, mortality, various mutation types, and lipid values can be provided. Further, the FH registries are important for improvements in diagnostics and therapeutics and to patient health care planning (143). Currently there are only a few national FH registries established. Apart from national FH registries, international FH registries are important to enhance the care of FH worldwide (143).

Concluding remarks and future perspectives

The present studies underscore the importance of earliest possible FH diagnosis and optimal preventive treatment in order to achieve recommended lipid treatment targets to reduce the present high CVD morbidity and CVD mortality in this patient group. During the course of this PhD thesis many new interesting questions and perspectives have arisen. As discussed, the awareness of FH is low in Norwegian hospitals and the majority of FH patients are still undiagnosed. The main challenge is to identify the FH patients. To overcome this important issue, the National UCCG Registry could be directly linked to the hospital medical record systems as it seems as so many genotyped FH patients are not aware of reporting having FH at time of hospital admittance, and many physicians are unaware of FH not asking the patients. As FH is one of the most common inherited disorders, screening at birth may be an option to identify the index patients and their young relatives by cascade screening. Further, a specific diagnostic ICD-10 code for FH would increase the awareness of this condition.

New pharmaceuticals, such as the PCSK9 antibodies, represent important treatment options for significant LDL-C reduction in FH patients in addition to statins. The main question is whether a normalization of LDL-C by use of these new pharmaceuticals really can eliminate the risk of premature CVD events and premature CVD deaths in this patient group. Currently there are not sufficient data to answer this question, or whether FH patients in the future will attain the same risk of CVD as in the corresponding general Norwegian population.

MAIN CONCLUSIONS

Paper I

The CVD mortality was significantly higher in all FH patients < 70 years of age based on the main underlying cause of death compared with the general Norwegian population. Overall there were no significant differences in all-cause mortality or cancer mortality in FH patients compared with the corresponding general population. Mean age at time of death was 61.1 years. The majority of the deceased FH patients did not reach recommended LDL-C target values. There were no significant differences in mutation types in the deceased FH patients compared to the mutation types in the FH-cohort.

Paper II

At time of death, 93% of the FH patients had established CVD. The mean age at first CVD event was 44 years, and the mean age at the time of death was 60 years with no significant sex differences in age at the first CVD event or age at the time of death. CVD was the cause of 50% of the deaths, and 69% had experienced one or more MIs. More of the younger FH patients (< 60 years of age) received statins and fewer received niacin compared with the older patients (> 60 years). The majority of the deceased FH patients did not reach recommended LDL-C treatment targets, and the last measured LDL-C level was higher in the younger patients compared with the older FH patients. There were more current smokers among the younger FH patients compared with the older patients.

Paper III

Most CVD hospitalizations were due to IHD which was reported in 90% of all hospitalizations. More FH men than FH women were hospitalized of which most hospitalizations were in the age group 40-59 years. There were no sex differences in mean age at first hospitalization (45.1 years) or in re-hospitalizations (47.6 years). In the FH cohort about 25% of all patients were hospitalized due to CVD, and 80% were re-hospitalized. Most hospitalizations were elective admissions. For comorbidity CHD was most common (46.8%) followed by ACS (25.2%) and hypertension (20.7%). Comorbidity due to heart failure, aortic aneurysms and atrial fibrillation/flutter were higher in FH men than FH women. The

awareness of FH in Norwegian somatic hospitals was reportedly low. Despite having an existing FH diagnosis at time of hospital admission, the FH diagnosis was registered in only 45.7% of the patients at discharge.

Paper IV

All FH patients < 70 years of age had significantly higher CVD mortality compared with the general Norwegian population, including all underlying, contributory and immediate causes of death. There were significantly more CVD deaths occurring out-of-hospital in FH patients < 70 years of age compared with the corresponding general population. In patients < 40 years of age the risk for total CVD deaths out-of-hospital was >12-fold increased in FH patients. No significant differences in special circumstances were reported in FH patients compared with the corresponding general population. In spite of genotyped FH and premature CVD deaths, the majority of all death certificates did not include FH among any of the contributing causes of death.

Appendix

Table A1. Previous FH studies on mortality and CVD morbidity by use of National FH- registries. Characteristics of articles and summary of results

Country	Reference and publication year	National FH registry used	Study type and sample size, n	Age (years)	Male N, (%)	Follow-up time (years)	FH-diagnosis: clinical or genetically verified FH	Number of patients on statins, (%)	Main outcome measure	Risk measure used	Main findings
Denmark	Jensen et al.(82) 1967	11 Danish families	Family study N=181 hypercholesterolemic members	10-79 years	84(46.4)	1943-1964	Clinical FH	0	All-cause mortality in FH	SMR(95%CI) ²	SMR total: 2.18 (1.9-2.5)* SMR men: 2.88 (1.8-4.5)* SMR women: 1.71 (1.0-2.9)* *calculated 95% CIs PMR total :10.9 (8.0-15.0)* *calculated 95%CI
Japan	Mabuchi et al.(83) 1986	Japanese FH national centers Registry	Cohort study N=527 patients with heterozygous FH	All ages	-	1976-1986	Clinical FH	0	CHD ¹ mortality in FH	PMR(95%CI) ²	
United Kingdom	The Simon Broome Register Group.(33) 1991	Simon Broome Register	Cohort study N=526 with heterozygous FH	20-74 years	282(53.6)	1980-1989	Clinical FH	0	CHD mortality in FH	SMR(95%CI) ²	SMR CHD total: 3.86 (2.10-6.39)
United Kingdom	The Simon Broome Register Group.(84) 1999	Simon Broome Register	Cohort study N=1185 with heterozygous FH	20-79 years	605(51.1)	1980-1995	Clinical FH	86% on statins from January 1, 1992	All-cause mortality CHD mortality in FH Cancer mortality in FH	SMR(95%CI) ²	SMR all-cause total: 1.83(1.7-2.73) SMR CHDmen:2.6(1.7-3.8) SMR CHD women: 3.7(2.3-5.8) Age 20-39 years: SMR CHD women: 125(15.1-451.3) SMR CHD men: 48.4(17.8-105.5) Age 20-59 years: 1980-1991:SMR CHD 8.0(4.8-7.2) 1992-1995: SMR CHD 3.7(1.6-7.2) SMR cancer total:0.81(0.47-1.32) Overall prevalence:
United	Neill et	Simon	Prospective	All ages	162(48.5)	1980-June	Clinical FH	-	Prevalence of	Prevalence of	

Kingdom	al.(85) 2000	Broome Register	registry study N=334 with FH	30,1999		diagnosed FH in patients resident in Oxfordshire	FH per 1000 (95%CI)	0.54/1000(0.48-0.60). Prevalence was highest in men 50-59 years: 1.28/1000(and in women 60-69 years: 1.83/1000
The Netherlands	Sijbrands et al. (86) 2000	Dutch Lipid clinics Registry	Family tree study N=855 first degree relatives of 113 Dutch index FH patients	1988-1990	426(49.8)	Clinical FH	SMR(95%CI) ²	SMR total: 1.34(1.16-1.55) in all first degree relatives
The Netherlands	Sijbrands et al. (38) 2001	Dutch Lipid clinics Registry	Pedigree analysis N=250	1830-1989	-	Genetically verified FH: descendants carrying LDL-R mutation(V408M)	SMR(95%CI) ²	SMR total:1.32(1.03-1.67) in all pedigree members
United Kingdom	Huxley et al.(87) 2003	Simon Broome Register	Prospective registry study N=2871 patients with heterozygous FH	1980-1998	1405(48.9)	Clinical FH	SMR(95%CI) ²	SMR total: 0.79(0.36-1.50) From 1992(on statins): SMR 0.93(0.40-1.83)
United Kingdom	Neil et al.(88) 2003	Simon Broome Register	Prospective registry study N=2871 patients with heterozygous FH (N= 1569 with xanthomatous FH (TX +) /N=1302 non xanthomatous FH (TX -)	1980-1998	1405(48.9) TX + : 774(49.3) TX- : 631(48.5)	Clinical FH	SMR(95%CI) ²	SMR TX+ total:294 (228-380) and SMR TX- total:205 (145-282)
The Netherlands	Nolling De Sauvage et al. (89) 2003	Dutch Lipid clinics Registry	Cohort study/cross-sectional study N=526 with FH	-	55.6 %	Clinical FH/genetically verified in 62% of the cases	OR(95%CI) ³	OR Male gender:1.70(1.05-2.76) OR age: 1.10(1.08-1.13) OR hypertension:1.82(1.03-3.22) OR BMI ⁹ :1.07(1.00-1.14) OR HDL-C:0.39(0.19-0.80)
The Netherlands	Jansen et al. (90) 2004	Dutch Lipid clinic registry	Cohort study N=2400 N=782 with	1999-2002	CVD+62 % CVD-	Genetically verified FH	RR(95%CI) ⁵	RR male gender:2.82(2.37-3.36) RR smoking: 1.67(1.40-

CVD(CVD+)/N=16
18 without
CVD(CVD-)

:42.8%

1.99)
RR hypertension:
1.36(1.06-1.75)
RRdiabetes:2.19(1.36-
3.54)
RRlowHDL:1.37(1.15-
1.63)
RR Lp(a):RR1.50(1.20-
1.79)

The Netherlands	Mohrschladt et al.(91) 2004	Dutch Lipid Clinics Registry	N=345 with FH N=214 in primary prevention N=131 in secondary prevention	0-79 years	1988-1997	Clinical FH	89% continuously on statins	CVD mortality IHD ⁵ mortality All-cause mortality Total mortality	RR(95%CI) ⁶	RR all-cause mortality men:1.5(1.0-2.3), women 1.0(0.5-1.9) Primary prevention: RR CVD mortality total: 1.4 (0.6-3), and total 4.3 (1.6-11) (40-59years), RR (IHD mortality) total: 2.6(1.1-6.3), and 7.6(2.9-20) (40-59 Years) Female FH patients had no increased CVD or IHD mortality risk
United Kingdom	Neill et al.(92) 2005	Simon Broome Register	Cohort study N=2871 with heterozygous FH	0-79 years	1980-1998	Clinical FH	At registration 54.6% on cholesterol-lowering drugs	CHD mortality All-cause mortality Non-CHD Cancer mortality Stroke mortality Accidents and violence mortality	SMR(95%CI) ²	SMR CHD total: 2.5(2.1-3.1).SMR all-cause total: 1.1(0.9-1.3) SMR non-C HD total: 0.6 (0.4-0.7) SMR cancer total:0.6(0.4-0.8) SMR stoke total:0.8 (0.4-1.5) SMR accidents and violence total:0.6(0.2-1.5)
United Kingdom	Neill et al.(93) 2008	Simon Broome Register	A prospective registry study N=3382 with Heterozygous FH	20-79 years	1980-2006	Clinical FH	N= 54.6% were on lipid lowering drugs Statins were available from January 1, 1992	CHD mortality Stroke mortality Non-coronary heart disease(NCH) Accidents and violence (A&V) All-cause mortality Cancer mortality	SMR(95%CI) ² from January 1, 1980-December 31, 1991 SMR (95%) ² from January 1, 1992-2006	Before 1992 total: SMR CHD: 339(238-467) SMR Stroke:36(1-198) SMR NCH: 61(36-97) SMR A&V:43(1-240) SMR cancer: 96(53-161) SMR all cause: 137(103-178) After 1992 total:

The Netherlands	Vermissen et al (94) 2008	Dutch Lipid clinic Registry	Cohort study N= 2146 with FH Without prevalent CHD in primary prevention	-	48%	1989-2002	Clinical FH	After January 1, 1990 statins were initiated. 87% were on statins	Risk of CHD in treated patients with statins versus untreated Risk of MI in statins treated patients versus age matched sample from general population	HR (95%CI) ⁷	Risk reduction CHD with statins:76%,HR 0.24(0.18-0.30) HR MI: 1.44(0.80-2.60)
Japan	Yamashita et al (95) 2008	Japanese FH national centers Registry	Cohort study N= 410 with heterozygous FH (N= 322 patients in primary prevention group, N=88 in secondary prevention group)	27-74 years (primary prevention group 23-71 (secondary prevention group	134 (41.6%) primary prevention group 53(60.2%) secondary prevention	1984-1999	Clinical FH	80% on Probucol in primary prevention group 93% on Probucol in secondary prevention group	Time to first CVD event leading to hospitalization or death by use of Probucol in primary and secondary prevention	HR (95%CI) ⁷	HR primary prevention: 1.5(0.48-4.67) HR secondary prevention: 0.13(0.05-0.34)
Spain	Alonso et al (96) 2008	Spanish National FH Register	Cross-sectional study N=811 with heterozygous FH	>18 years of age	383(47.2)	-	Genetically Verified in patients with clinical FH with score 6 and more according to the Dutch Lipid clinic criteria.	> 80 % on statins	Risk of premature CVD/first CVD event occurring <55 years in men and <65 years of age in women) in FH patients in relation to type of LDLR mutation: receptor –negative mutation versus receptor-defective mutation Predictors of CVD in FH	OR (95%CI) ³	Risk of premature CVD, receptor-negative mutations OR: 1.68(1.10-2.40), recurrence of CVD events and family history of premature CVD in first degree relatives, OR: 1.67(1.20-2.3) Predictors of CVD total: male gender OR: 1.98(1.09-3.56) Smoking: OR 1.80(1.03-3.16) TC/HDL-C: OR: 1.26(1.01-1.58) Age OR: 1.05(1.02-1.07)

before 1992 and after January 1, 1992

SMR CHD: 213(181-250)
SMR stroke: 80(47-128)
SMR NCH: 62(53-72)
SMR A&V: 75(30-154)
SMR cancer: 63(60-79)
SMR all cause: 94(84-105)

The Netherlands	Vermissen et al.(97) 2011	Dutch Lipid clinics Registry	Pedigree study N=161 with FH	-	-	1830-1990	Genetically verified FH, carriers with the V408M mutation	-	All-cause mortality. Maternally inherited FH versus FH transmitted by fathers	SMR(95%CI) ²	SMR of maternally inheritance: 2.49(1.45-3.99) SMR of paternally inheritance : 1.30(0.65-2.32)
Spain	Mata et al.(98) 2011	Spanish National FH Register	Cohort study (SAFEHEART) N= 1 852 with FH	20-79 years of age	47.5 %	2004-2010	Genetically verified FH in N=1262 patients	84% on lipid-lowering drugs	Lipid lowering therapy associated with attainment of target: LDL-C<100 mg/dl	OR (95%CI) ³	OR combined therapy (statins and ezetimibe):2.22(1.10-4.48) adjusted for age, sex, CVD and CVD risk factors
South-Africa	Raal et al.(99) 2011	South Africa Lipid clinics Registry	Cohort study N=149 with homozygous FH	-	68(45.6)	1972-2009	Genetically verified N= 128 /N= 21 with clinical FH	Statins initiated in all patients at time of diagnosis after January 1, 1990, of which 88% received high- dose statins	CVD mortality and major adverse CVD events by use of statins versus non-statins	HR(95%CI)	CVD mortality:0.34(0.14-0.86) Major adverse CVD events:0.49(0.22-1.07)
The Netherlands	Besseling et al.(100) 2014	Dutch national screening program	Cohort study N=14,283 with heterozygous FH	0-93.7 years	48 %	1994-2013	100% Molecular defined FH	37.7% on lipid-lowering therapy	CVD risk in severe FH; (LDC-C 8 mmol/L and above) versus non severe FH Risk factors for CVD	HR(95%CI) ⁷	HR CVD risk severe FH versus non-severe FH: 1.25(1.05-1.51) OR male gender: 2.44(2.07-2.88) OR age: 1.08(1.08-1.09) OR BMI: 1.04(1.03-1.06) OR smoking: 1.59(1.36-1.86) OR hypertension: 2.38(2.01-2.82) OR diabetes: 1.37(1.03-1.82) OR HDL-C: 0.61(0.48-0.77) OR LDL-C:1.08(1.04-1.12)

¹CHD, coronary heart disease

²PMR, proportional mortality ratio, ² SMR, standardized mortality ratio. Mortality in the FH cohort is compared with the mortality in the general population in the same country by indirect standardization according to age and sex and calendar year.

³OR, odds ratio

⁴CVD, cardiovascular disease


⁵IHD, ischemic heart disease

⁶RR, relative risk

⁷HR, hazard ratio

⁸BMI: body mass index (kg/m²)

Table A2. The requisition form to genetic test for FH in Norway

 Oslo universitetssykehus Rekvisisjon til gentesting for familær hyperkolesterolemi Enhet for hjertegenetikk Postboks 4956 Nydalen, 0424 Oslo Tlf: 22118991/22118975 e-post: medgenlab@oslo-universitetssykehus.no	Personnr.:	
	Etternavn:	Fornavn:
	Adresse:	
	Postnr:	Poststed:
	Tlf.:	
	Kommune:	Dato:
For laboratoriet:	ID nr.	1 2 3 4 5 6 Fam. nr. 7 8 9 10 11 12

Poliklinisk Innliggende

Uten behandling:

Lipidverdier før ev. kolesterolsenkende behandling ble startet:	
Årstall	<input type="text"/>
Totalkolesterol	_____ mmol/l
HDL-kolesterol	_____ mmol/l
Triglyserider	_____ mmol/l
Fastende prøve	<input type="checkbox"/> Ja <input type="checkbox"/> Nei

Lipidanalyser:

Sist målte verdier:

Sist målte verdier:	
Årstall	<input type="text"/>
Totalkolesterol	_____ mmol/l
HDL-kolesterol	_____ mmol/l
Triglyserider	_____ mmol/l
Fastende prøve?	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Kolesterolsenkende medikamenter ved de sist målte verdier	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Hvis Ja – før på medikament og dose:	

Har pasienten:

Xantomer:	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Xantelasmer:	<input type="checkbox"/> Ja <input type="checkbox"/> Nei
Annen sykdom: (beskriv sykdom, debutår og behandling)	

Hjerte-karsykdom	år, debut
Angina pectoris	<input type="checkbox"/> Ja <input type="checkbox"/> Nei <input type="text"/>
Hjerteinfarkt	<input type="checkbox"/> Ja <input type="checkbox"/> Nei <input type="text"/>
Perifer karsykdom	<input type="checkbox"/> Ja <input type="checkbox"/> Nei <input type="text"/>
Andre opplysninger:	

Rekvirerende lege:

Etternavn:	Fornavn:
Adresse:	Tlf.:
Postnr:	Poststed:

Veiledning til utfylling av slekts opplysningene

Slektsopplysningene på neste side skal brukes til å vurdere sannsynligheten for at det foreligger arvelig høyt kolesterol. En slik vurdering er nødvendig for å planlegge de genetiske undersøkelsene. I tillegg vil opplysningene eventuelt danne grunnlag for å gi råd om hvilke andre familiemedlemmer som også kan ha risiko for å ha arvelig høyt kolesterol.

Det er viktig at skjemaet fylles ut så fullstendig som mulig, men vi er klar over at det kan være vanskelig å skaffe helt presise opplysninger om alle slektingene.

Man bes opplyse hvem det er i familien som har eller har hatt hjerteinfarkt eller angina pectoris og i hvilken alder dette inntreffe. Vi har også behov for informasjon om hvem det er i familien som har fått påvist høyt kolesterolnivå i blodet, men like viktig er det å få opplyst hvem det er som har helt normalt kolesterolnivå. Før derfor på kolesterolverdien på så mange av slektingene som mulig. Vi har primært behov for verdier **før** eventuelt kolesterolsenkende behandling ble startet. Det er bedre med omtrentlige verdier enn ingen verdier.

Hvis andre i slekten allerede har fått påvist en genfeil (mutasjon) som årsak til arvelig høyt kolesterol, må det opplyses om hvem dette er og navnet på genfeilen.

NB! Vi trenger ca 5 ml EDTA-blod (helst vacutainer av plast). Blodprøven sendes usentrifugert. Pasienten skal signere på neste side.

SLEKTSOPPLYSNINGER – fyll ut så godt du kan

Navn	Fødselsdato eller -år, evt. -sted	Opplysninger om hjerte-, karsykdom, kolesterolverdi og evt. resultat av gentest
Din far:		13
Din mor:		
Din farfar:		
Din farmor:		
Din morfar:		
Din mormor:		
Dine søsken:		
1		
2		14
3		15
4		16
5		
Dine barn:		
1		
2		17
3		18
4		19
5		
Din fars søsken:		
1		

2		20
3		21
4		22
5		
Din mors søsken:		
1		
2		23
3		24
4		25
5		
Andre opplysninger (fortsett evt. på eget ark)		
Samtykke: Undertegnede samtykker i at det tas blodprøve til genetisk diagnostikk med tanke på arvelig høyt kolesterol.	Dato:	Underskrift:

It has come to my attention that unfortunately there are two minor errors in two of the mortality analyses performed in paper I, entitled *Mortality among patients with familial hypercholesterolemia: A registry-based study in Norway, 1992-2010*, by Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierod MB, Leren TP, Retterstol K, published in *J Am Heart Assoc* 2014;3:e001236. There are two values in the two published Tables 5 and 6 for number of observed deaths, SMRs and 95% CIs in both genders combined in age groups 0 to 69 years of concern that are corrected in the revised tables enclosed below. However, these minor errors do not change the main results in paper I.

Table 5. Cancer mortality in the UCCG Registry

Attained age (years)	Observed deaths	Expected deaths	SMR	95% CI
Both genders				
0-19	0	0.19		
20-39	2	1.36		
40-59	10	13.26	0.75	0.41-1.40
60-69	12	15.45	0.78	0.44-1.37
70-79	6	12.33	0.49	0.22-1.08
> 80	5	4.05	1.23	0.51-2.96
Total	35	46.65	0.75	0.54-1.05
0-69	24	30.27	0.79	0.53-1.18
Men				
0-19	0	0.11		
20-39	0	0.57		
40-59	5	5.76	0.87	0.36-2.09
60-69	8	8.11	0.99	0.49-1.97
70-79	4	6.28	0.64	0.24-1.70
> 80	4	1.45	2.76	1.03-7.35
Total	21	22.28	0.94	0.61-1.45
0-69	13	14.55	0.89	0.52-1.54
Women				
0-19	0	0.09		
20-39	2	0.79	2.52	0.63-10.07
40-59	5	7.50	0.67	0.28-1.60
60-69	4	7.34	0.55	0.20-1.45

70-79	2	6.05	0.33	0.08-1.32
> 80	1	2.60	0.38	0.05-2.73
Total	14	24.37	0.57	0.34-0.97
0-69	11	15.72	0.70	0.39-1.26

SMR indicates standardized mortality ratio.

Table 6. Death by other causes in the UCCG Registry

Attained age (years)	Observed deaths	Expected deaths	SMR	95% CI
Both genders				
0-19	2	1.40	1.42	0.36-5.70
20-39	4	7.02	0.57	0.21-1.52
40-59	8	13.36	0.60	0.30-1.20
60-69	3	9.55	0.31*	0.10-0.97
70-79	3	10.78	0.28
> 80	6	7.92	0.76	0.34-1.69
Total	26	50.04	0.52*	0.35-0.76
0-69	17	31.34	0.54*	0.34-0.87
Men				
0-19	2	0.98	2.03	0.51-8.14
20-39	3	5.10	0.59	0.19-1.82
40-59	3	8.74	0.34	0.11-1.06
60-69	2	5.69	0.35	0.09-1.41
70-79	0	5.24
> 80	2	2.03	0.98	0.25-3.93

Total	12	27.80	0.43*	0.25-0.76
0-69	10	20.52	0.49*	0.26-0.91
Women				
0-19	0	0.42	0.00
20-49	1	1.91	0.52	0.07-3.71
40-59	5	4.63	1.08	0.45-2.60
60-69	1	3.86	0.26	0.04-1.84
70-79	3	5.53	0.54	0.17-1.68
> 80	4	5.89	0.68	0.25-1.81
Total	14	22.24	0.63	0.37-1.06
0-69	7	10.82	0.65	0.31-1.36

SMR indicates standardized mortality ratio. * P <0.05.

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