Mortality for individuals with familial hypercholesterolemia (FH) in the period 1992 to 2010

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Master of Science Thesis in Clinical Nutrition

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May 2012

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A registry-based study

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ABSTRACT:

BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is an autosomal dominantly inherited disorder of lipid metabolism, caused predominantly by mutations in the LDL receptor (LDLR) gene. Hypercholesterolemia, increased low-density lipoprotein cholesterol (LDL-C) and increased total cholesterol are associated with an increased risk of cardio vascular diseases (CVD). Increased prevalence of CVD is associated with sudden premature death. Modern dietary and drug treatment have been associated with lower levels of LDL and total cholesterol. The primary aim of this study was to determine the mortality causes in the period 1992-2010, for the individuals that are diagnosed with FH. The secondary aim of this study was to investigate the prevalence of death by CVD among FH individuals with consideration of age, gender and death cause. The CVD death causes that will be under consideration are myocardial infarction (MI), cerebral infarction and aortic aneurysm.

STUDY DESIGN: The Medical Genetics Laboratory at Oslo University Hospital, has a FH registry. At endpoint the FH registry had 4688 individuals. The FH registry was linked to The Norwegian Cause of Death Registry. This linked registry contained 113 observed deaths. A cohort of men and women aged 0-59, were followed from 1992 to 2010. They were followed for 29853 person years. Expected number of deaths was estimated by multiplying the gender, age and calendar specific deaths rates to the person years accumulated in the age and gender cohort. Deaths rates were estimated from the Norwegian population. Standardized mortality rate (SMR) was expressed as the ratio between observed deaths and number of expected deaths. Significance was defined by the 95% confidence interval (CI).

RESULTS: 46% of individuals with FH died of CVD. 30.1% died of cancer. The average age for death by CVD was 62.2 years. Women who died of CVD had an average death age of 67.2 years. For men average death age by CVD was 57.2 years. 71.2% of deaths by CVD were MI. SMR for death by CVD was 8.0 for the age group 30-39. For the age group 50-59, the SMR for death by CVD was 1.4. In the age 0-59 the SMR for death by CVD was significant with 2.1.

CONCLUSION: At age 0-59, cancer and none-CVD death cause had lower total SMR among FH individuals, than the general population. Individuals with FH have higher prevalence of death by CVD, than the general population. The main death cause by CVD is MI. Women had a 10 years higher average age of death by CVD than men. At age 0-59, individuals with FH have a higher SMR of death by CVD, than the general population.

ACKNOWLEDGEMENTS

This master thesis presents a contribution to the knowledge on mortality outcomes to persons diagnosed with FH. The thesis has been conducted from August 2011 to May 2012 at the Department of Nutrition, Faculty of Medicine, University of Oslo.

I am very grateful for being given the opportunity to work with this master thesis.

I am thankful to dr.med Kjetil Retterstøl, for including me in this study. Big thanks to dr.med Kjetil Retterstøl for his comments, talks and scientific contributions. Without his supervisor teaching this thesis would not have been possible.

Thanks to my supervisors dr.med Trond Leren and prof. Marit Veierød for the scientific advices.

I would also like to thank the workers from the Molecular genetic laboratory, University Hospital in Oslo for making the FH registry. Thanks to the workers for the Norwegian public health institute for making The Norwegian Cause of Death Registry. Without these to registries this master thesis would not have been possible.

Thanks to my family and friends for the encouragement during the study period. They have been a big inspiration for me.

Oslo, May 2012

Mirza Sarancic

CONTENTS

ABSTRACT…….....3

ACKNOWLEDGEMENTS…….……4

CONTENTS……...5

LIST OF ABBREVIATIONS……..8

1. BACKGROUND…….....10

1.1 HYPERCHOLESTEROLEMIA…….…...10

1.1.1 Inflammation and atherosclerosis……11

1.1.2 Risk factors for atherosclerosis and CVD…….……11

1.2 FAMILIAL HYPERCHOLESTEROLEMIA…….…...13

1.2.1 Genetics.....….....13

1.2.2 Frequency……..14

1.2.3 Diagnosis…….....14

1.2.4 Management of FH……...15

1.3 METHODOLOGICAL PROBLEMS IN FH MORTALITY……...….18

1.3.1 Challenges in assessment of FH mortality……19

1.4 FH AND DEATH CAUSES ……21

1.4.1 FH and myocardial infarction……...21

1.4.2 FH and cerebral infarction……...22

1.4.3 FH and aortic aneurysm…….…….…….22

1.5 AIMS OF THE STUDY…….....23

1.5.1 Problems to address regarding FH and mortality…….....23

1.5.2 Aims…….....23

2. SUBJECTS AND METHODS……...24

2.1 STUDY DESIGN AND DATA COLLECTION……..24

2.2 STUDY POPULATION…….....25

2.3 CATEGORIZATION OF THE DEATH CAUSES……...……26

2.4 STATISTICS…….……30

2.5 ETHICS……..30

3. RESULTS……....31

3.1 DESCRIPTION OF TOTAL MORTALITY…….31

3.2 DESCRIPTION OF TOTAL MORTALITY WITH CONSIDERATION OF GENDER AND AGE…….....33

3.3 ANALYSIS OF NONE CVD MORTALITY…….....35

3.4 ANALYSIS OF NONE CVD MORTALITY WITH CONSIDERATION OF GENDER AND AGE……...……..…36

3.5 DESCRIPTION OF CVD MORTALITY.....…..38

3.6 DESCRIPTION OF CVD MORTALITY WITH CONSIDERATION OF GENDER AND AGE.....….....39

3.7 ANALYSIS OF CVD MORTALITY…….....42

3.8 ANALYSIS OF CVD MORTALITY WITH CONSIDERATION OF GENDER AND AGE ……...42

3.9 ANALYSIS OF MORTALITY BY CVD WITH CONSIDERATION OF PERODIC INTERVALS…….....43

4. DISCUSSION.....…..44

4.1 CHALLENGES IN THE STUDY…….…….....44

4.2 METHODOLOGICAL CONSIDERATIONS...…… …..……47

4.3 GENERAL DISCUSSION……....49

4.4 PRINCIPAL FINDINGS.....52

4.5 FUTURE PERSPECTIVE .....…..54

5. CONCLUSION……55

6. REFERENCE LIST……56

7. APPENDIX……..68

APPENDIX 1: APPROVAL FROM THE REGIONAL ETHIC COMMITTEE…….68

APPENDIX 2: FORMULA FOR INTERNAL REGISTRATION. INTERNAL CONTROLL AND SETTLING OF RESEARCH RESPONSIBILITY…….71

APPENDIX 3: DEFINITION OF EXPECTED DEATH AGE……78

APPENDIX 4: PREVALENCE OF THE GENERAL POPULATION……..79

APPENDIX 5: PREVALENCE OF CVD DEATH IN THE GENERAL POPULATION……..80

APPENDIX 6: PREVALENCE OF CVD DEATH AMONG GENDERS IN THE GENERAL POPULATION…….81

List of Abbreviations

AAA	Abdominal aortic aneurysm
ARH	Autosomal recessive hypercholesterolemia
ATP	Adenosine triphosphate
Apo A-1	Apo lipoprotein A1
ApoB	Apo lipoprotein B
CHD	Coronary heart disease
CVD	Cardiovascular disease
CI	Confidence interval
EF	Error factor
EGF-A	Epidermal Growth Factor-Like Repeat A
FH	Familial hypercholesterolemia
HDL	High- density lipoprotein
HDL-C	High- density lipoprotein cholesterol
HMG CoA	Hydromethylglutaryl Co-enzyme A
ICD	International Classification of Diseases
IDL	Intermediated density lipoprotein
IHD	Ischaemic heart disease
LDL	Low- density lipoprotein
LDL-C	Low- density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	LDL receptor adaptor protein 1
LPL	Lipoprotein lipase

MGL	Medical Genetics Laboratory
MI	Myocardial infarction
PCSK 9	Proprotein convertase subtilisin/kexin type 9
PPAR	Perixisome proliferator- activated receptor
SES	Socioeconomic status
SMR	Standardized mortality rate
SR-B	Scavenger receptors class B
SREBP-2	Sterol regulatory element binding protein-2
SPSS	Statistical Package of Social Sciences
TAA	Thoracic aortic aneurysm
TG	Triglyceride
VLDL	Very low- density lipoprotein
VCAM-1	Vascular cell adhesion molecule-1
WHO	World health organization

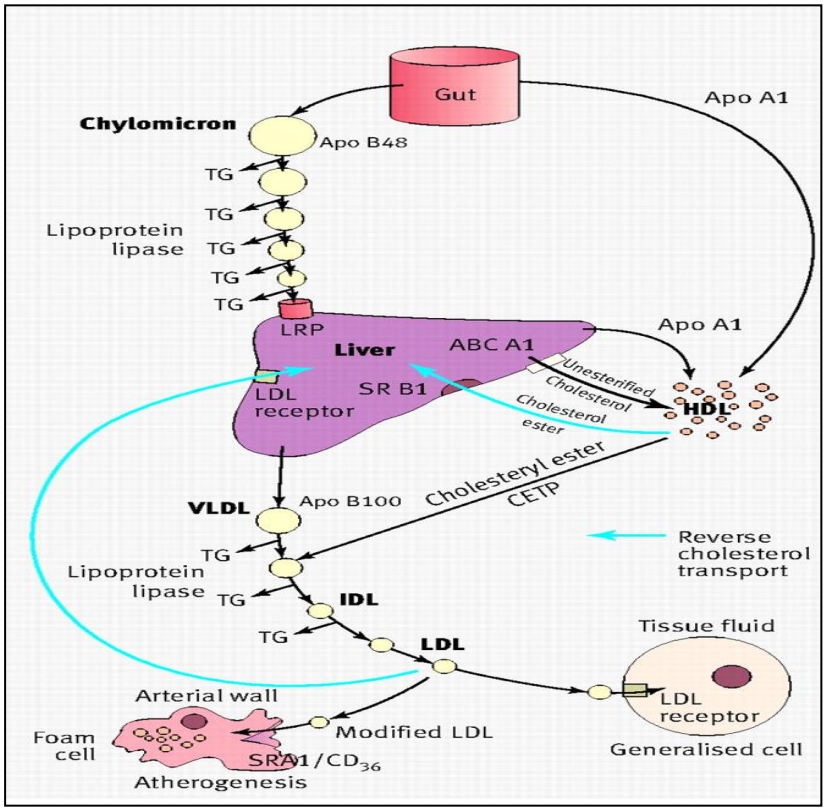
1. BACKGROUND

1.1 Hypercholesterolemia

Cholesterol can be synthesized de novo in the liver, gut and the central nervous system (1). Cholesterol is essential to life. It is the primary component of cell membranes and a substrate for the synthesis of bile acids, steroid hormones and vitamin D (2).

Hypercholesterolemia is usually induced by a combination of genetic and lifestyle factors. To avoid hypercholesterolemia it is important that the metabolism of cholesterol is in a normal biologically way (1).

Figure 1.0 Dietary cholesterol pathway (1).



Dietary cholesterol is absorbed in the gut. Chylomicrons are rich in triglycerides (TGs) and transport the dietary cholesterol to the live (3). In the liver cholesterol and TGs get modified. The liver secretes very low density lipoprotein (VLDL). Lipoprotein lipase (LPL) and hepatic lipase converts VLDL to intermediate density lipoprotein (IDL) and later to low density lipoprotein (LDL) (3, 4).

LDL distributes cholesterol to the body tissues. The uptake of LDL into the tissue cells is induced by LDLR (3).

Cells remove excessive cholesterol by high density lipoprotein (HDL). HDL transports excessive cholesterol back to the liver for degradation. Cholesterol is excreted through the bile as bile acids and free cholesterol (1). HDL can be taken up directly in the liver by scavenger receptors class B (SR-B). Some of the HDL gets transferred to VLDL and LDL by the enzyme cholesteryl ester transfer protein. It is then taken up to the liver by LDLR (3).

Two major groups of lipoproteins are important in the cholesterol metabolism. Apolipoprotein B (ApoB) is an important part of the chylomicrons, VLDL, IDL and LDL, while Apolipoprotein A1 (Apo A-1) is mainly found in HDL (3).

1.1.1 Inflammation and atherosclerosis

Atherosclerosis was characterized as artery formed lipid deposits (5). Now we have better knowledge about the atherosclerosis process and understand that inflammation plays a role(6).

Hypercholesterolemia promotes the inflammatory process. During the development of atherosclerosis leukocytes attach to the arterial wall by the vascular cell adhesion molecule-1(VCAM-1) (4). Oxidized lipids can induce VCAM -1 expression. The macrophages express scavenger receptors for modified lipoproteins. This permits macrophages to ingest lipids and become foam cells in the arterial wall (4).

1.1.2 Risk factors for atherosclerosis and CVD

Gender

Studies suggest that women have 0.25-0.3 mmol/l higher levels of HDL than men (7). It is assumed that the difference in levels of HDL, between the genders is caused by the estrogen hormone (7). A prospective study of 14786 Finnish individuals aged 25-64 years, suggested that the prevalence of coronary mortality was 5 times higher in men than in women (8).

Smoking

Smoking increases the risk for coronary heart disease (CHD) in both men and women. The risk of CHD increases with number of cigarettes (9). Smokers have lower levels of HDL cholesterol (HDL-C). Some studies suggest that smokers have 14% lower HDL levels, than none smokers (10).

Age

Aging is linked with increasing prevalence of atherosclerosis and CVD. 71% of Norwegian men, who died of CVD in 2006, were over 75 years old. 90% of Norwegian women, who died of CVD in 2006, were over 75 years old (11).

Diabetes

Type 2 diabetes mellitus is associated with a marked increase in the risk of atherosclerotic disease. Adults with type 2 diabetes mellitus are up to four times more likely than individuals without the disease, to suffer from cardiovascular events (12). It is assumed that insulin resistance can increase the prevalence of CVD by dyslipidemia, hypertension and inflammation (13).

Hypertension

Hypertension is a risk factor for the development of atherosclerosis. It is assumed that hypertension can induce inflammation on the arterial walls (14). Hypertension is associated with an increased risk of morbidity and mortality from cerebral infarction, CHD and MI (15). There is often a prevalence of insulin resistance in hypertensive patients (16).

Abdominal obesity

Visceral fat is linked with higher levels of LDL and total cholesterol. Lower levels of HDL-C and increased prevalence of insulin resistance is also associated with visceral fat. Substances released by visceral fat, enter the portal vein and travel to the liver, where they can influence the production of blood lipids (17, 18). Visceral fat segregates free fatty acids, cytokines, tumor necrosis factor, interleukin-6 and adiponectin. High segregation of these substances can increase the risk of CVD by promoting insulin resistance and inflammation (17, 18).

Physical activity

Physical activity is important to reduce hypertension, diabetes and obesity (19). 5-13% of the risk for hypertension can be prevented by physical activity (20). Increased energy spender and utilization of fat are some of the health gains of physical activity. Physical activity can also decrease the prevalence of insulin resistance (19).

Stress

Stress can promote an unhealthy behavior like smoking, lack of exercise, excessive alcohol consumption and an unhealthy diet. Stressors can promote CVD through the segregation of hormones. Hormones like cortisol and adrenalin can affect the heart rhythm and the contraction of blood vessels (21).

1.2 Familial hypercholesterolemia

1.2.1 Genetics

FH is an autosomal dominantly inherited lipid metabolism disorder (22).

Mutations in the LDLR-gene

Individuals with heterozygote FH have approximately 50% of the functioning LDLRs (23). FH homozygotes can have 0-25% of normal LDLR function (24).

There has been identified over 1000 different mutations in the LDLR gene (25). Among individuals in Norway, approximately 130 LDLR gene mutations have been found to cause FH (22).

There are five main classes of mutations in the LDL-R (26). In class one none LDLRs are synthesized. LDLR gets processed in the Golgi apparatus (27). Disruption in the transport from the endoplasmic reticulum to the Golgi apparatus is categorized in class two. In class three mutations, LDL-R fails to bind to the LDL at the cell surface. Failing of clustering of the LDLR into the coated pits after binding to the LDL are class four mutations (28, 29). Inside cells the ligand complex is transported to the endosomes, where the acidic environment causes dissociation of the receptor-ligand complex (27). The LDLR is recycled to the cell surface, while the LDL particle is degraded in the lysosomal compartment. Class five mutations prevent LDLRs from being recycled to the cell surface (28, 29).

Mutations in other genes than the LDLR-gene

Mutations in other genes than the LDLR gene can cause FH. Two of those gene mutations are ApoB and proprotein convertase subtilisin/kexin type 9 (PCSK9). Mutations in these genes are less common, than in the LDLR gene (27, 30).

ApoB is the major particle of the LDL. The LDLR binds to the LDL by ApoB (31). PCSK9 induces degradation of the LDLR-protein by binding to the Epidermal Growth Factor-Like Repeat A domain (EGF-A) (31). Mutations in the gene coding for the PCSK9 occur rarely (27).

1.2.2 Frequency

FH is under diagnosed. It is estimated that only about 20% of the FH cases are ascertained. Worldwide more than 10 million people have FH (22, 32).

The frequency of homozygote FH is one per 1000000 individuals. In most populations the frequency of heterozygote FH is approximately one per 500 individuals (22, 32). Some studies suggest that the Norwegian frequency of heterozygote FH is one per 313. It is estimated that approximately 15000 Norwegians have FH (33).

1.2.3 Diagnosis

FH is characterized by hypercholesterolemia, a total blood cholesterol level above 7.5mmol/l or a blood concentration of LDL-C above 4.9 mmol/l (34).

Table 1.0 Recommended blood levels of cholesterol for primary prevention of CVD. From the Norwegian Directorate of Health (11, 35, 36).

Cholesterol	Women	Men
Total-cholesterol	< 5.0 mmol/l	< 5.0 mmol/l
HDL-c	> 1.3 mmol/l	> 1.1 mmol/l
LDL-c	< 3.0 mmol/l	< 3.0 mmol/l
TG	< 1.7 mmol/l	< 1.7 mmol/l

To diagnose FH, hypercholesterolemia must be present together with xanthomatosis and a premature ischemic heart disease (IHD) history. The premature IHD history can be in the case or a close relative (34). Premature IHD history is by many defined as cardiovascular event occurring before 55 years among men and before 65 years among women (11).

Xanthomatosis is deposits of cholesterol in tendons and skin. The presence of xanthomas is correlated with a 3 times higher risk of CVD (37).

An alternative to the clinical criteria are DNA based analysis on LDLR, ApoB, and PCSK9 mutations (38).

1.2.4 Management of FH

Medical treatment

The mainly used drug treatments are statins. Statins provide reduction in plasma LDL by up regulating expression of LDLRs (39). Statins reduce the cholesterol production be inhibiting the enzyme 3-hydroksy-3-metylglutaryl-coenzym A (HMG-CoA)-reductase (40). HMG-CoA-reductase regulates the syntheses of cholesterol by controlling the transformation of HMG-CoA to mevalonic acid. This is the velocity determined step in the production of cholesterol (40). Sterol-regulatory element-binding protein 2 (SREBP-2) is a transcription factor, which gets activated when liver cells get deprived for cholesterol. SREBP-2 is a transcription factor for LDLR, HMG-CoA-reductase and 3-hydroxymethyl-3-glutaryl-(HMG-CoA) –synthase (40).

Studies suggest that statin prescription for FH individuals under 18 years can be beneficial in the prevention of atherosclerosis. Statin use did not indicate any adverse effect on growth and pubertal development. These studies prescribed a maximal dose of daily 40mg statin (41, 42, 43).

Ezetimibes and Bile acid sequestrants are mainly used when individuals experience statin intolerance or insufficient effect of statins.

Ezetimbe reduces the absorption of dietary and biliary cholesterol by preventing its transport through the intestinal wall. Current knowledge indicates that Ezetimibe has no effect on the absorption of fat soluble vitamins, fatty acids and bile acids (44, 45).

Bile acid sequestrants are often called resins. Bile acid sequestrants interrupt the enterohepatic circulation of bile acids and inhibit the absorption of bile acids from the intestine. As result the liver cells produce more LDLRs. Bile acid sequestrants significantly reduce total cholesterol and LDL-C. Caution needs to be taken in therapy with bile acid sequestrants because these drugs may interfere with the absorption of fat soluble vitamins and concurrent medication (39, 46).

Fibrates and Nicotinic acids/niacin are sometimes used in the treatment of FH. Fibrates act on peroxisome proliferator activated receptors (PPARs). Activation of PPARs causes transcription of a number of genes that facilitate lipid metabolism (46). Nicotinic acids /niacins have a modest effect on LDL-C. These drugs decrease the concentration of free fatty acids by inhibiting breakdown of adipose fat (46).

Dietary recommendations

Dietary advice should be given on addition to treatment with statins. Dietary changes should be combined with other lifestyle changes like daily exercise, smoking cessation and stress management (11, 34, 46).

Dietary intervention relies upon the reduction of LDL-C by replacing saturated fat with unsaturated fat. Some foods that contain unsaturated fats are nuts, fatty fish like salmon, mackerel and trout. Oils of raps, olive, soya and sunflower also contain unsaturated fatty acids. These foods should replace some of the saturated fat. Saturated fat is mainly found in bakery, diary and red meat products (11, 34, 46).

FH-individuals should be careful with consumption of cholesterol. Egg yolks are one of the biggest sources of cholesterol in food (11, 34, 46).

Plant sterols are assumed to reduce absorption of cholesterol. Plant sterols are mainly consumed as functional foods. It is also recommended with a nutrition that is rich in fiber. Fibers are mainly found in wholegrain (11, 34, 46).

When it is necessary it is important to indicate a diet for weight loss (11, 34, 46).

Table 1.1 Nutrient composition of the recommended FH diet in Norway (47, 48).

Nutrient	Recommended intake (of total energy intake)
Total fat	25 %
Saturated fat	< 7%
Trans fat	< 1%
Monounsaturated fat	10-15%
Polyunsaturated fat - **Omega-3**	5-10% 1%
Cholesterol	< 200mg per day
Protein	10-20%
Carbohydrat - **Sugar**	50-60% Max 10%
Fiber	25-35 g per day
Plant stanol/sterols	2 g per day

Special treatments

Special treatments are mainly used by individuals with homozygous FH. LDL apheresis and liver transplantation are the most known special treatments (49).

LDL apheresis is a mechanical method, similar to that used in kidney dialysis. The process is removing LDL-C from the blood. LDL apheresis needs to be undertaken approximately every one to two weeks by trained health workers (49).

Liver transplantation gives individuals new functioning liver cells that are able to process the LDL-C. There are considerable side effects attached with liver transplantation (49).

Effects of treatment

Scandinavian Simvastatin Survival Study suggests that statins are reducing mortality and morbidity in CHD patients (50). Statins can lower LDL-C by an average of 1.8mmol/l. This reduces the risk of IHD events by 60% and stroke by 17% (51).

Compared to alone statin treatment, combination of statin with bile acid sequestrants can reduce LDL-C by additionally 10-20% (52). Ezetimibe has largely replaced the use of bile acid sequestrants. When used as monotherapy, ezetimibe decreases LDL-C by about 18% (44, 45). Ezetimibe combined with any statin will provide a mean LDL-C reduction of 14 to 25% (44).

Several studies suggest that dietary recommendations can have impressive impact on lowering LDL-C. The mainly used polyunsaturated fatty acid replacements for saturated fatty acids are ω – 6. Some studies suggest that replacing 5% of the saturated fatty acids with polyunsaturated fatty acids decreases the ratio between total and HDL cholesterol by 0.17 (53).

A meta-analysis suggested that a daily intake of stanol /sterol enriched fat spreads significantly reduced total cholesterol by 7-11%. The study used stanol/sterol dosage of 2.3 g per day (54).

Recommended dietary fiber intake is suggested to reduce total cholesterol. In hypercholesterolemic and diabetic patients, soluble fibers with diet that is low at saturated fat and cholesterol, lowers LDL-C with 5-10 % (55, 56).

1.3 Methodological problems in FH mortality

For ethical reasons placebo controlled studies that measure mortality and hard endpoint, can not be conducted among individuals with FH (57). Little is known how long term statin treatment has affected morality among individuals with FH. An example of this is that in clinical trials statin treatment has been studied for no more than two years in FH children (58, 59). New data are needed for answering questions about how modern treatment affects the mortality prognosis.

Some individuals get FH diagnosed late in life. In early life years, these individuals are exposed for high cholesterol levels. It is unclear how high cholesterol levels before the introduction of treatment, has influenced the prevalence of death by CVD.

Previous studies

The time frame of the Simon Broome study in the early 1990s overlaps with the introduction of statins. This allows a comparison of SMR before and after the use of these medications. The relative risk of coronary mortality in patients aged 20–59 years was higher from 1980 to 1991, than from 1992. Simon Broome study suggested that statin treatment is effective in lowering the risk of death from CHD in individuals with FH (60).

2146 FH patients were in the Rotterdam study. FH patients received a mean daily dose of 33mg simvastatin or 49mg atorvastatin. A compared group did not receive treatment. In the Rotterdam study the risk of MI in the statin treated patients was not significantly greater than in an age matched sample from the general population. In the treated group, the Rotterdam study observed an overall risk reduction of MI by 76% (61).

1.3.1 Challenges in assessment of FH mortality.

Individuals who avoid treatment

Some FH individuals can not get treatment in some periods of life. It is unknown how these periods affect mortality and hard endpoints.

It is recommended for women during pregnancy to avoid statins (62). Statins have been linked to fetal abnormalities. It is assumed that first-trimester statin exposure can defect the central nervous system and make unilateral limb deficiencies. Ezetimbie and Niacin have in animal studies adverse effects on the fetus (63).

Some studies suggest that muscular side effects during exercise are related to statin treatment (64). A study monitored 22 professional athletes with FH for 8 years. The study suggested that only 20% of the professional athletes tolerated statin treatment without getting muscular side effects (65).

It is unclear how long term use of statin and other lipid lowering drugs can influence the development of malignant diseases. Most studies suggest that long term statin use is not associated with cancer (66, 67, 68, 69).

Gender

The Simon Broom study suggested that women aged 20-39, who were treated for FH, had an annual coronary mortality of 0.17%. For men in the same category the annual coronary mortality was 0.46%. For FH men and FH women aged 60-79 the annual mortality was 1.1% (60).

Age

A Japanese study observed 527 individuals with heterozygote FH. Individuals were examined over 10 years. 41 deaths were observed. The mean age of death from a cardiac event was

significantly younger among men. Men suffered from a cardiac event at average of 54 years, while women suffered from a cardiac event at average of 68 years (70, 71).

Differences in national nutrition policy

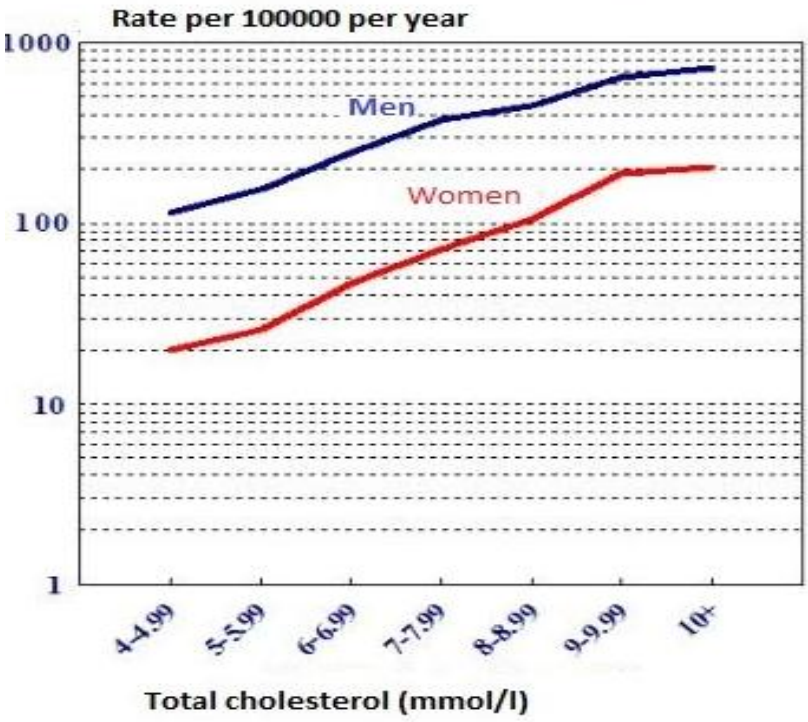
CVD is responsible of about 50% of all deaths in Europe. CVD is the main contributor to the 20 year difference, in life expectancy across Europe (72).

One example of how national nutrition policy can affect prevalence of CVD mortality is the North Karelia project. The North Karelia project brought dietary changes to a local population in Finland (72). The project primary targeted changes in smoking and dietary habits. The results of the North Karelia project suggested that reducing risk factors can have a dramatic effect on CHD mortality. In 35 years, the annual age adjusted CHD mortality rate among the 35- 64 year old male population in North Karelia declined with 85% (73).

1.4 FH and death causes

It has been estimated that 200000 individuals with FH, die of CHD each year (22). Increased total cholesterol levels are associated with CVD. Increased prevalence of CVD is associated with increased sudden premature death (74).

Figure 1.1 Increased cholesterol increase the risk of death by MI and IHD (74 , 75). Logarithmical graph describes the rate of death by MI and other IHD with consideration of cholesterol levels. Deaths are calculated as rate per 100000 per year (75).



It is estimated that 50% of men that are untreated for heterozygote FH, will get CVD before 50 years of age. Before 60 years of age 50% of women that are untreated for heterozygote FH, will get CVD (76). The life age for both genders is estimated to be reduced between 20-30 years (77).

1.4.1 FH and myocardial infarction (MI)

Studies before the statin treatment decade suggest that individuals with untreated FH are 11 times at greater risk for CHD death than the general population (70). Before the introduction of statins, some studies suggested that about 70% of deaths among FH individuals were from CHD (70, 71). Some studies suggest that since the introduction of statin treatment, CHD mortality has significantly reduced by 37% among FH individuals (78). Other studies suggest

that the risk of MI in statin treated patients was not significantly greater than in an age matched sample from the general population (61). In 1994 among the Norwegian population, 20.5% of women and 26.8% of men died of MI (79).

1.4.2 FH and cerebral infarction

Kaste et al conducted a study before the treatment with statins was introduced. They suggested that individuals with FH have 20 times higher risk of cerebral infarction than the general population (80, 81). Other studies suggest that FH individuals with statin treatment are not at higher risk of fatal stroke than the general population (82). Cerebral infarction is the third most prevalent death cause in Norway. In 1999, 12% of the Norwegian population died from cerebral infarction (79).

1.4.3 FH and Aortic aneurysm

In western countries ruptured abdominal aortic aneurysm (AAA) is the cause of 1-2 % of all deaths (83). Men, smokers and individuals with increasing age are at higher risk for AAA, but increased cholesterol levels, hypertension and low HDL levels also increases the prevalence of AAA (84).

1.5 Aims of the study

1.5.1 Problems to address regarding FH and mortality

High LDL and total cholesterol levels are associated with increased risk of CVD (74, 75). High prevalence of CVD is associated with increased premature mortality (85). Individuals with FH are at risk for high LDL and total cholesterol. Modern dietary interventions and drug treatments have been associated with lower levels of LDL and total cholesterol (11, 51). We have little knowledge about how modern treatment has affected the CVD morality prognosis. It can be assumed that premature mortality among individuals that have been diagnosed with FH has been reduced the last years. There is need for more knowledge about the relationship between FH and mortality.

1.5.2 Aims

The aims of this study were to investigate:

- The mortality causes in the period 1992-2010, for the individuals who are diagnosed with FH.
- The prevalence of death by CVD among FH individuals with consideration of age, gender and death cause. The CVD death causes that will be under consideration are MI, cerebral infarction and aortic aneurysm.

2. SUBJECTS AND METHODS

2.1 Study design and data collection

The data was derived from patient lists at the Medical Genetics Laboratory (MGL) and The Norwegian Cause of Death Registry.

Registries

Molecular genetic testing for FH has been available in Norway since 1998 at a national MGL in Oslo University Hospital. Per December 2010 there were registered over 23000 patients of which 4688 with diagnosis of FH.

The Norwegian Cause of Death Registry is a population based registry of all causes of death since 1951 (86). Doctors are required to complete a death certificate of all reported deaths. Death certificates are collected by the Cause of Death Registry. The coding system used in the death certificates is the International Classification of Diseases (ICD). ICD is used by the world health organization (WHO) (87). This international system allows us to follow development of various causes of death and to compare mortality causes between different countries. Currently the 10th revision of ICD is being used.

Norwegian Cause of Death Registry and the FH registry were linked by the governmental statistical bureau.

Table 2.0 Variables from the linked registry

Categorical variables	Continuous variables	Other variables
• Gender • The death cause • The reliability of the diagnosis • Diagnose 2 • Diagnose 3 • Diagnose 4 • Diagnose 5 • The place of mortality • Death in institution • The commune were the case lived	• Datum of mortality • Year of mortality • Age of death	• The circumstances of death 1 • The circumstances of death 2

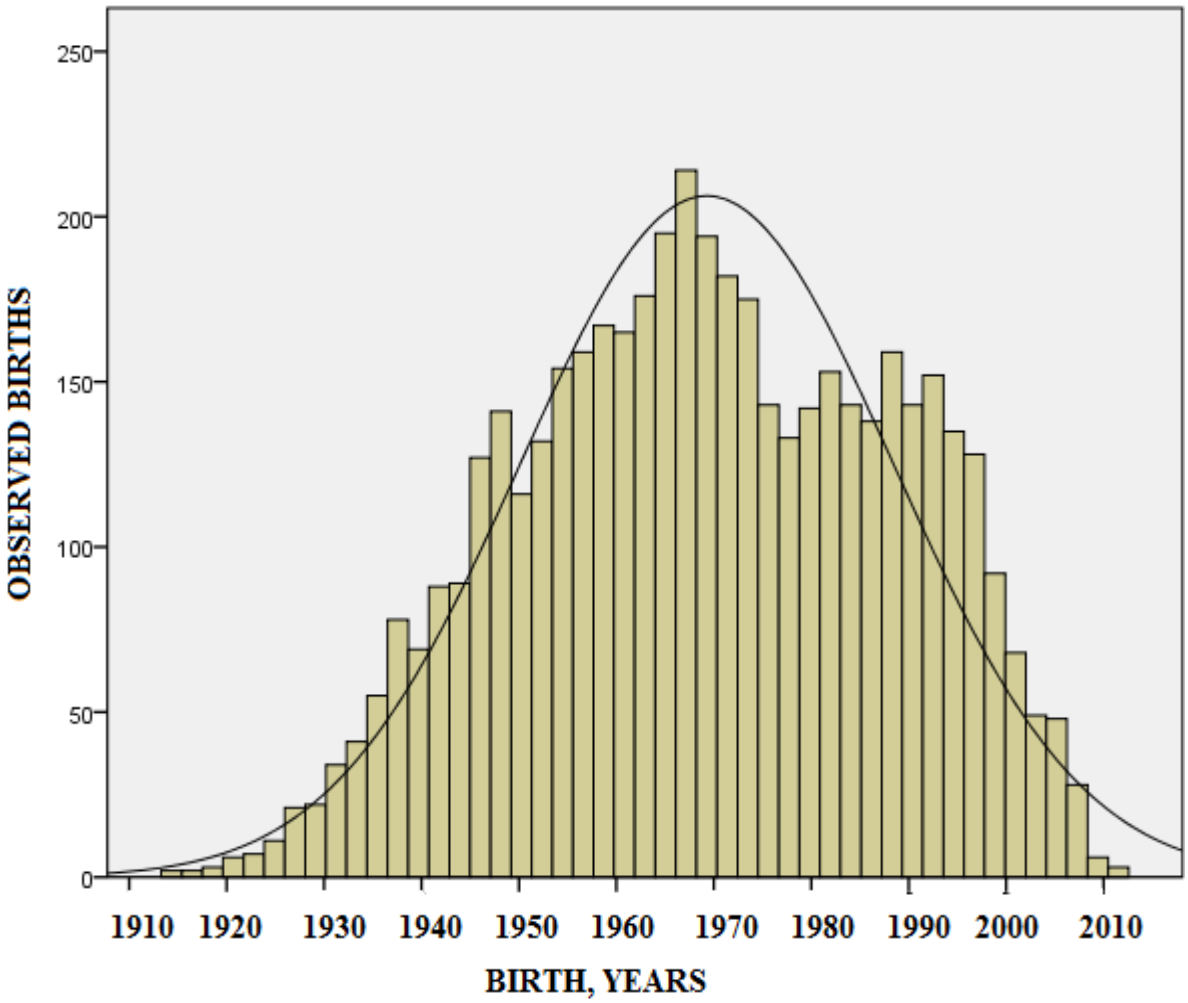
2.2 Study population

At the study endpoint, the FH registry contained 4688 individuals. Of the 4688 individuals 2238 were men and 2450 were women. The linked registry contained 113 observed deaths.

The birth year of the individuals in the FH registry, suggest that the FH registry has an approximate normal distribution of age.

The average age in the FH registry was 41.6 years. The youngest person in the FH registry was 110 days old. The oldest person in the FH registry was 94.7 years. Five persons were under one year of age, while six persons were over 90 years of age.

Figure 2.0 Distribution of birth year in the FH registry.



2.3 Categorization of the death causes

Three cases were coded with ICD-9. Rest of the cases was coded with ICD-10. We categorized death causes into the following categories:

1. Death by CVD
2. Death by cancer
3. Death by other causes
4. Death by possible CVD

CVD death causes were categorized into following categories:

1. Death by MI
2. Death by cerebral infarction
3. Death by Aortic aneurysm
4. Death by possible MI

Table 2.1 ICD-codes that were interpreted as death by CVD. Categorized CVD death causes (87, 88, 89).

ICD codes	Description	CVD categorization
I21.9	Acute myocardial infarction, unspecified	MI
I22.9	Subsequent myocardial infarction of unspecified site	MI
I24.8	Other forms of acute ischemic heart disease	MI
I25.1	Atherosclerotic heart disease	MI
I25.2	Old myocardial infarction	MI
I25.8	Other forms of chronic ischaemic heart disease	MI
I25.9	Chronic ischaemic heart disease, unspecified	MI
I26.9	Pulmonary embolism without mention of acute cor pulmonale	Possible MI
I35.0	Aortic (valve) stenosis	Aortic aneurysm
I35.1	Aortic (valve) insufficiency	Aortic aneurysm
I38	Endocarditis, valve unspecified	Possible MI
I48	Atrial fibrillation and flutter	Possible MI
I50.1	Left ventricular failure	MI
I51.7	Cardiomegaly	Possible MI
I51.9	Heart disease, unspecified	MI
I60.9	Subarachnoid haemorrhage, unspecified	Cerebral infarction
I62.0	Subdural haemorrhage (acute) (nontraumatic)	Cerebral infarction
I63.9	Cerebral infarction, unspecified.	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction	Cerebral infarction
I71.1	Thoracic aortic aneurysm, ruptured	Aortic aneurysm
I73.9	Peripheral vascular disease, unspecified Claudicatio intermittens	MI
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities	Possible MI
E78.0	Pure hypercholesterolaemia	MI
410(ICD-9)	Acute myocardial infarction	MI

Table 2.2 ICD-codes that were interpreted as death by cancer (87, 88, 89).

ICD codes	Description
C06.9	Mouth, unspecified
C18.0	Caecum
C18.9	Colon, unspecified
C20	Malignant neoplasm of rectum
C22.1	Intrahepatic bile duct carcinoma
C26.9	Ill-defined sites within the digestive system
C34.1	Upper lobe, bronchus or lung
C34.9	Bronchus or lung, unspecified
C43.6	Malignant melanoma of upper limb, including shoulder
C43.9	Malignant melanoma of skin, unspecified
C50.9	Breast, unspecified
C53.9	Cervix uteri, unspecified
C56	Malignant neoplasm of ovary
C61	Malignant neoplasm of prostate
C71.2	Temporal lobe
C74.9	Adrenal gland, unspecified
C80	Malignant neoplasm, without specification of site
C91.1	Chronic lymphocytic leukaemia of B-cell type
147(ICD-9)	Pharynx
191(ICD-9)	Malignant neoplasm of brain

Table 2.3 ICD-codes that were interpreted as death by other causes (87, 88, 89).

ICD codes	Description
A 40.1	Sepsis due to streptococcus, group B
A41.9	Sepsis, unspecified
G30.9	Alzheimer's disease, unspecified
G31.9	Degenerative disease of nervous system, unspecified
G40.9	Epilepsy, unspecified
G71.3	Mitochondrial myopathy, not elsewhere classified
K26.4	Duodenal ulcer
K57.8	Diverticular disease of intestine, part unspecified, with perforation and abscess
K81.9	Cholecystitis, unspecified
R54	Senility
R99.9	Other ill-defined and unspecified causes of mortality
V23.4	Motorcycle rider injured in collision with car, pick-up truck or van
V48.5	Car occupant injured in noncollision transport accident
W15	Fall from cliff
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
X44	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X59.0	Exposure to unspecified factor causing fracture
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
Y08	Assault by other specified means

Table 2.4 ICD-codes that were interpreted as death by possible CVD (87, 88, 89).

ICD codes	Description
E10.9	Insulin-dependent diabetes mellitus without complications
E14.9	Unspecified diabetes mellitus without complications
W10.0	Fall on and from stairs and steps

2.4 Statistics

The analyses were performed using The Statistical Package of Social Sciences (SPSS) version 19.0. Some of the analysis was performed by using Microsoft Excel.

Descriptive statistics was used to describe the frequency of the gender and age.

Person years are the estimation between when a person was included in the FH registry and when that person reached endpoint.

The age and calendar specific deaths rates for men and women in the Norwegian population were found from the governmental statistical bureau. Expected number of deaths was estimated by multiplying the gender, age and calendar specific deaths rates to the person years accumulated in the age and gender cohort (60, 90).

SMR was derived from the ratio of the number of observed deaths, to the number of expected deaths (60, 90). SMR was calculated by indirect standardization.

Absolute risks of mortality were calculated per 100000 person years.

95% CI was used to determine statistical significance. 95 % CI was calculated with the mathematical equation 95% CI= SMR/EF to SMR x EF where EF stands for error factor. EF= exponential (1.96/ √observed number of deaths). If 95% CI contained number 1, then the SMR was considered as none significant (90). Significant 95% CI is assumed to give a significance with a p-value <0.05 (90).

2.5 Ethics

The study was approved by The Regional Ethic Committee (appendix 1) and by Oslo University Hospital for internal control and settling of research responsibility (appendix 2).

3. RESULTS

3.1 Description of total mortality

The linked registry contained 113 observed deaths. 46.0% of observed deaths were from CVD. The next highest death cause was cancer with 30.1%. Deaths by other causes like accidents and unspecified sepsis represented 20.4% of the observed deaths. Death by possible CVD was responsible for 2.7% of observed deaths.

Table 3.0 Observed deaths.

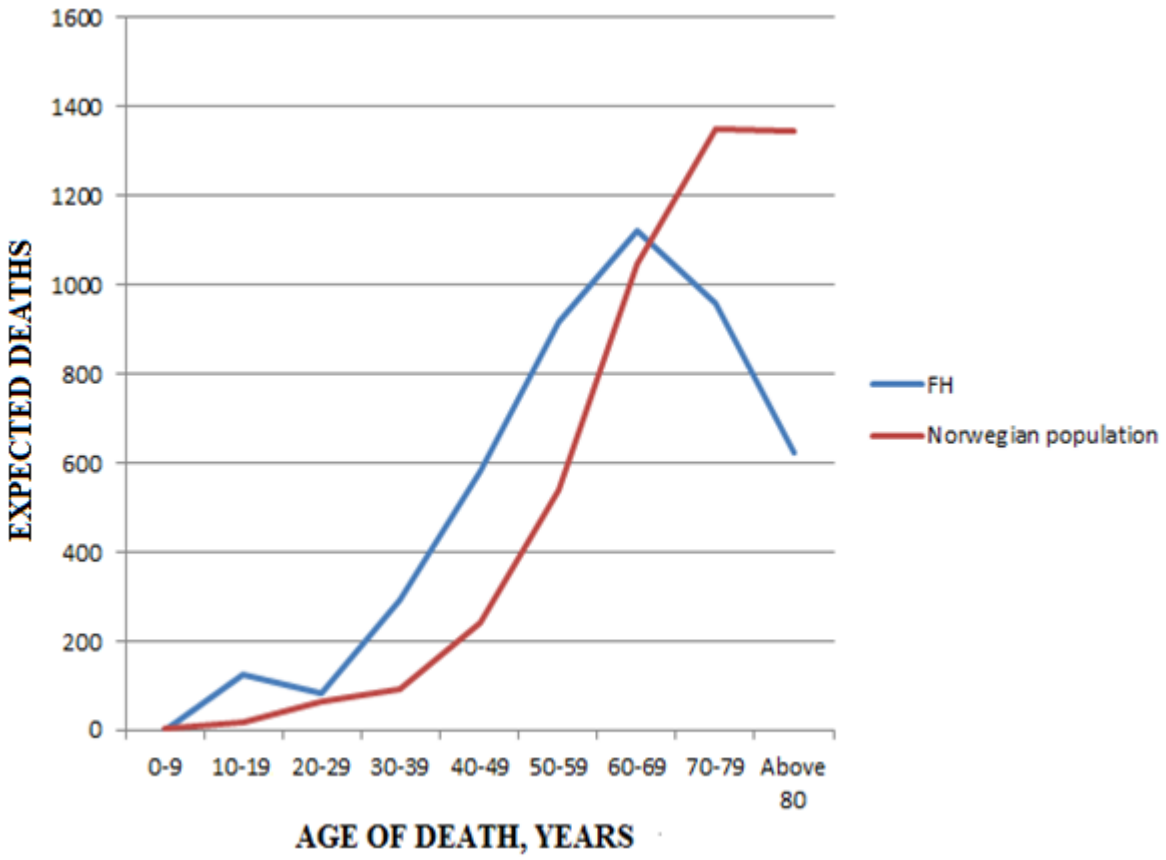
	Observed deaths	Percent
Death by CVD	52	46.0
Death by cancer	34	30.1
Death by other causes	24	21.2
Death by possible CVD	3	2.7
Total	113	100.0

The age of death among the 113 observed deaths were wide spreading. The youngest death of age was 18 years, while the oldest was 94 years. This represents a life year difference in 76 years. The average age of death was 61.1 years.

Figure 3.0 Age of death among all death causes.

The FH population had a peak for excepted death around 60 years. The general Norwegian population had a peak for expected death around 80 years. The prevalence of expected death was higher among the FH population than the general Norwegian population in the age 0-60. In the age after 60 the prevalence of expected death was higher among the general Norwegian population, than the FH population.

Figure 3.1 Expected deaths among FH and the general Norwegian population. This figure compares expected death for 4666 persons from the FH registry with 4666 persons from the general Norwegian population. Expected deaths for the general Norwegian population were calculated as described in section 2.4. Expected deaths for 10 years age groups were divided with total expected deaths. Numbers from each age group were multiplied with 4666. The same estimates were calculated for the FH population. For the FH population the estimates were calculated from observed deaths.



3.2 Description of total mortality with consideration of gender and age

The linked registry had a composition of 59 dead men and 54 dead women. This indicates an equal gender composition.

Table 3.1 Observed deaths among genders.

Gender	Observed deaths	Percent
Men	59	52.2
Women	54	47.8
Both genders	113	100.0

For men the average age of death was 58.1 years. The lowest death age among men was 18 years. The highest death age among men was 85 years.

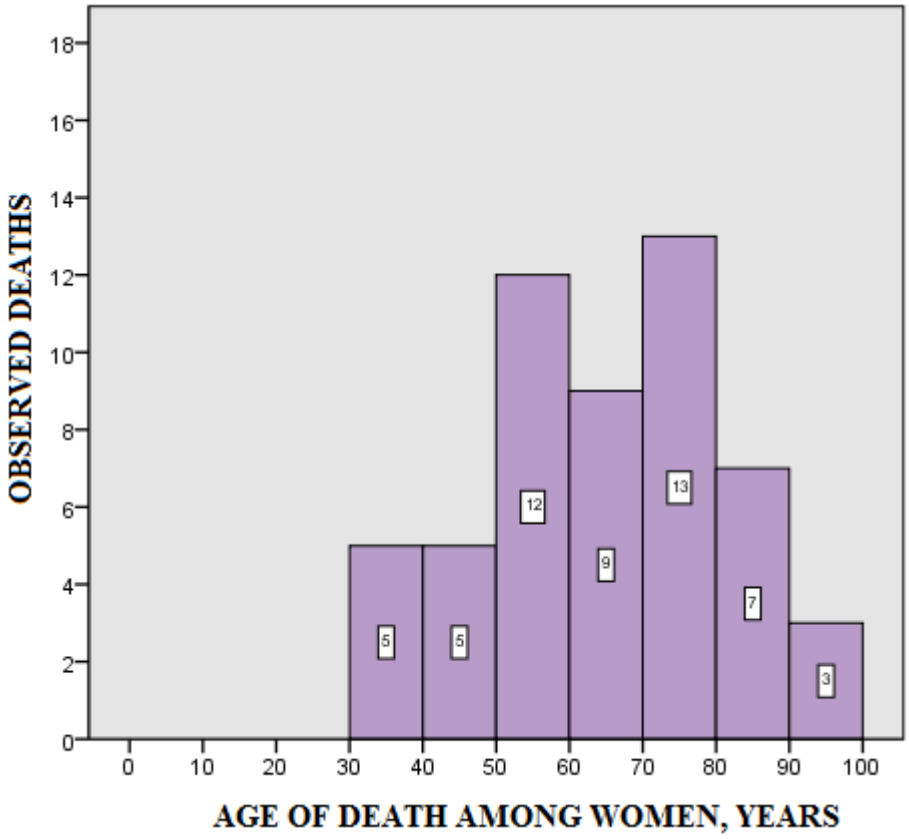
For women the average age of death was 64.4 years. The lowest death age among women was 31 years, while the highest death age among women was 94 years.

Table 3.2 Age of death among genders.

	Mean	Minimum	Maximum	Lower 95% CI	Upper 95% CI
Men	58.1	18	85	53.7	62.5
Women	64.4	31	94	60.0	68.9
Both genders	61.1	18	94	58.0	64.3

Figure 3.2 Age of death among men.

Figure 3.3 Age of death among women.



All the cases that died before 30 years of age were men. None of these cases died of CVD.

Table 3.21 Cases that died before 30 years of age.

ICD-code	Description	Age of death	Gender
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	20	Men
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	24	Men
W15	Fall from cliff	19	Men
V48.5	Car occupant injured in noncollision transport accident	19	Men
V23.4	Motorcycle rider injured in collision with car, pick-up truck or van	18	Men

All the cases that died after 85 years of age were women. There were five cases that died after 85 years of age. Of these four persons died of CVD.

Table 3.22 Cases that died after 85 years of age.

ICD-code	Description	Age of death	Gender
I48	Atrial fibrillation and flutter	89	Women
I35.0	Aortic (valve) stenosis	90	Women
I63.9	Cerebral infarction, unspecified	91	Women
R54	Senility	94	Women
I38	Endocarditis, valve unspecified	87	Women

3.3 Analysis of none CVD mortality

None CVD mortality

None CVD mortality had 26 observed deaths for age 0-59. In the age group 10-19 did FH individuals have higher SMR, than the general population for none CVD death. Total SMR for none CVD mortality for age 0-59 was significant with 0.6.

Table 3.3 Mortality analysis: None-CVD mortality both genders
(All ICD-10 codes besides I00-99).

Attained age	Person-years of observation	Observed deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
0-9	461	0	0.2	0.0	0	0
10-19	3093	3	0.8	3.8*	1.2-11.8	97
20-29	5726	2	3.6	0.6	0.2-2.4	35
30-39	6265	3	4.8	0.6	0.2-1.9	48
40-49	7533	6	11.0	0.5	0.2-1.1	80
50-59	6775	12	23.1	0.5*	0.3-0.9	177
Total	29853	26	43.5	0.6*	0.4-0.9	87

*** p<0.05**

Cancer

Cancer had 11 observed deaths in the age 0-59. In the age 0-29, there were none observed deaths by cancer. In the age group 30-39 did FH individuals have higher SMR for deaths by cancer, than the general population. Total SMR for cancer mortality at age 0-59 was 0.6.

Table 3.31 Mortality analysis: Cancer both genders (ICD-10 codes C00-97 and D00-47).

Attained age	Person-years of observation	Observed deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
0-9	461	0	0.0	0.0	0	0
10-19	3093	0	0.1	0.0	0	0
20-29	5726	0	0.3	0.0	0	0
30-39	6265	2	1.1	1.8	0.5-7.2	32
40-49	7533	2	4.7	0.4	0.1-1.6	27
50-59	6775	7	13.3	0.5	0.2-1.1	103
Total	29853	11	19.5	0.6	0.3-1.1	37

*** p<0.05**

3.4 Analysis of none CVD mortality with consideration of gender and age

None CVD mortality

None observed CVD deaths were among women, in the age group 0-19. It was 13 observed deaths for none CVD mortality among women. For men it was observed 13 none CVD deaths. Men in the age group 0-19 and women in the age group 20-39 had higher SMR for none CVD death, than the general population. Total SMR for none CVD mortality among men in the age 0-59 was significant with 0.5. Total SMR for none CVD mortality among women in the age 0-59 was 0.7.

Table 3.4 Mortality analysis: None-CVD with consideration of genders (All ICD-10 codes besides I00-I99).

Attained age	Person-years of observation	Observed Deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
Men						
0-19	1946	3	0.9	3.3*	1.1-10.2	154
20-39	5806	2	5.6	0.4	0.1-1.6	34
40-59	6980	8	18.7	0.4*	0.2-0.8	115
Total	14732	13	25.2	0.5*	0.3-0.9	88
Women						
0-19	1608	0	0.5	0.0	0	0
20-39	6185	3	2.6	1.2	0.4-3.7	49
40-59	7328	10	14.8	0.7	0.4-1.3	136
Total	15121	13	17.9	0.7	0.4-1.2	86

*** p<0.05**

Cancer

In the age 0-59 there was 3 observed deaths among men and 8 among women for death by cancer. In the age 0-39, there were none observed deaths by cancer among men. The mortality analysis with consideration of gender suggests that women in the age group 20-39 have higher SMR, than the general population for death by cancer. For death by cancer men in the age 0-59 had a significant total SMR with 0.3. For women in the same age group SMR for death by cancer was 0.8.

Table 3.41 Mortality analysis: Cancer with consideration of gender (ICD-10 codes C00-97 and D00-47).

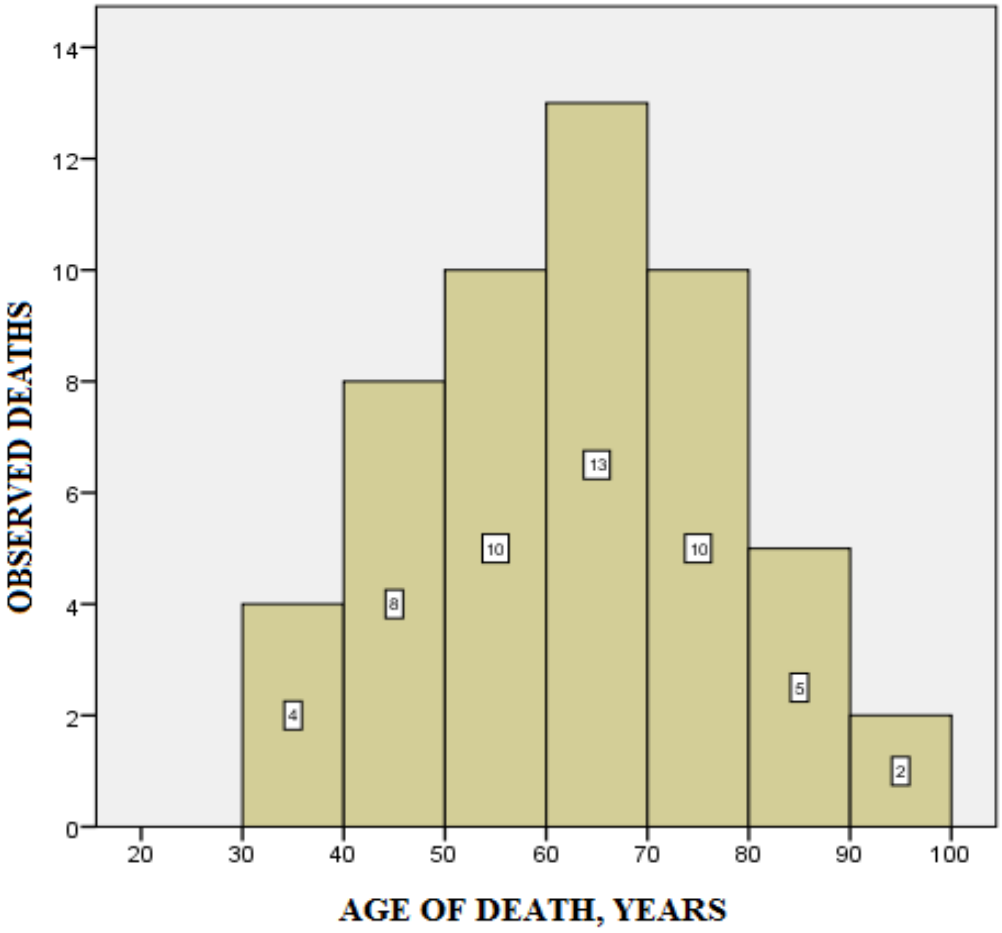
Attained age	Person-years of observation	Observed Deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
Men						
0-19	1946	0	0.1	0.0	0	0
20-39	5806	0	0.6	0.0	0	0
40-59	6980	3	8.0	0.4	0.1-1.2	43
Total	14732	3	8.7	0.3*****	0.1-0.9	20
Women						
0-19	1608	0	0.1	0.0	0	0
20-39	6185	2	0.8	2.5	0.6-10.0	32
40-59	7328	6	9.6	0.6	0.3-1.3	82
Total	15121	8	10.5	0.8	0.4-1.6	53

*** p<0.05**

3.5 Description of CVD mortality

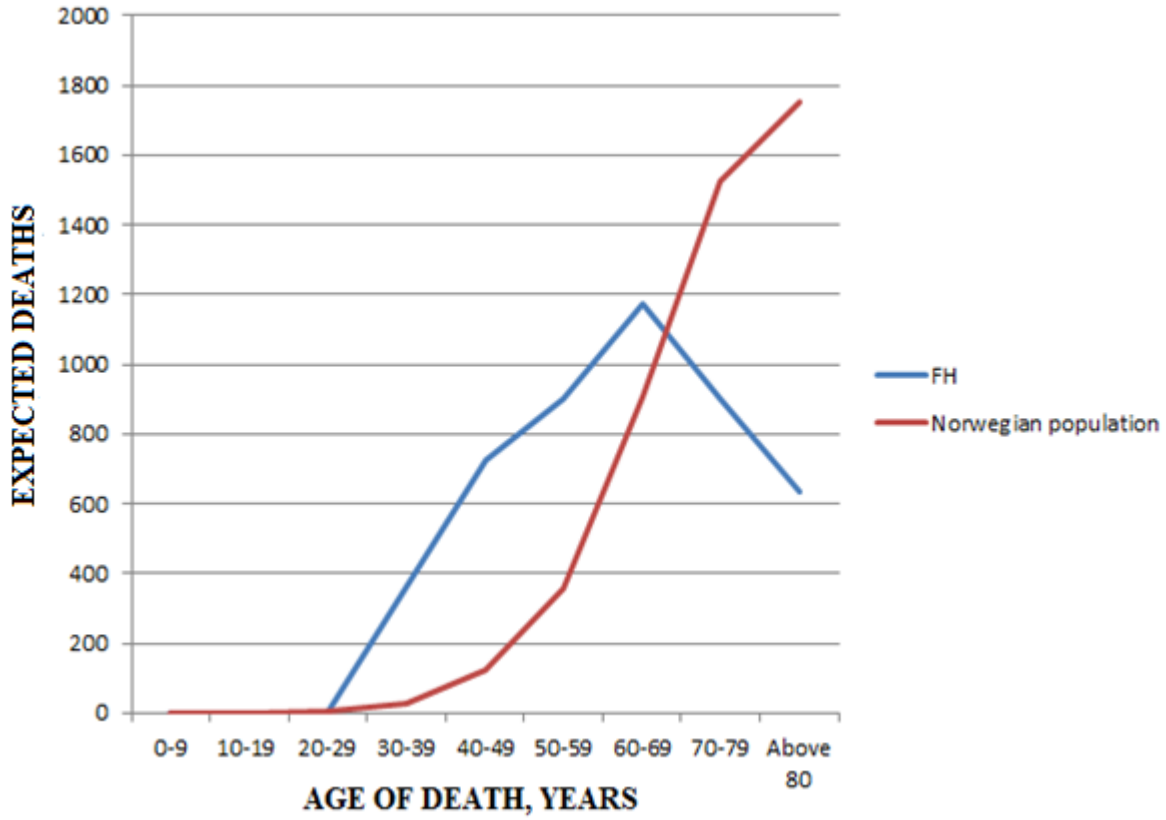
52 persons died of CVD. The average age of death by CVD was 62.2 years. Most persons died of CVD in the age group 60-69. It was 12 CVD deaths in the age 30-49, while it was 7 CVD deaths in the age 80-99.

Figure 3.4 Age of death among CVD deaths.



The FH population had a peak of around 60 years for expected CVD death. The general Norwegian population had a peak of around 80 years for expected CVD deaths. The prevalence of expected CVD deaths was higher among the FH population than the general Norwegian population in the approximant age 25-60. In the age after 60 the prevalence of expected CVD deaths was higher among the general Norwegian population compared to the FH population.

Figure 3.5 Expected CVD deaths among FH and the general Norwegian population. This figure compares expected CVD death for 4666 persons from the FH registry with 4666 persons from the general Norwegian population. The figure was calculated by the same method as figure 3.1.



3.6 Description of CVD mortality with consideration of gender and age.

Both men and women had 26 observed CVD deaths.

Table 3.5 Observed CVD deaths among genders.

	Observed CVD deaths	Percent
Men	26	50.0
Women	26	50.0
Both genders	52	100.0

37 observed deaths were from MI. It represented 71.2% of total CVD mortality. Six persons died of cerebral infarction and three died of aortic aneurysm.

Table 3.6 Categorized CVD deaths among both genders.

Death causes	Observed deaths	Percent
Both genders		
Death cause by MI	37	71.2
Death by cerebral infarction	6	11.5
Death by Aortic aneurysm	3	5.8
Possible MI	6	11.5
Total	52	100.0

84.6% of CVD deaths among men were from MI. There were 22 observed MI deaths among men. One man died of cerebral infarction while two men died of aortic aneurysm.

Table 3.61 Categorized CVD deaths among men.

Death causes	Observed deaths	Percent
Men		
Death cause by MI	22	84.6
Death by cerebral infarction	1	3.9
Death by Aortic aneurysm	2	7.7
Possible MI	1	3.9
Total	26	100.0

15 women died of MI. This represented 57.7% of CVD mortality among women. One woman died of aortic aneurysm. 19.2% of CVD mortality among women was from cerebral infarction. 5 women died of cerebral infarction.

Table 3.62 Categorized CVD deaths among women.

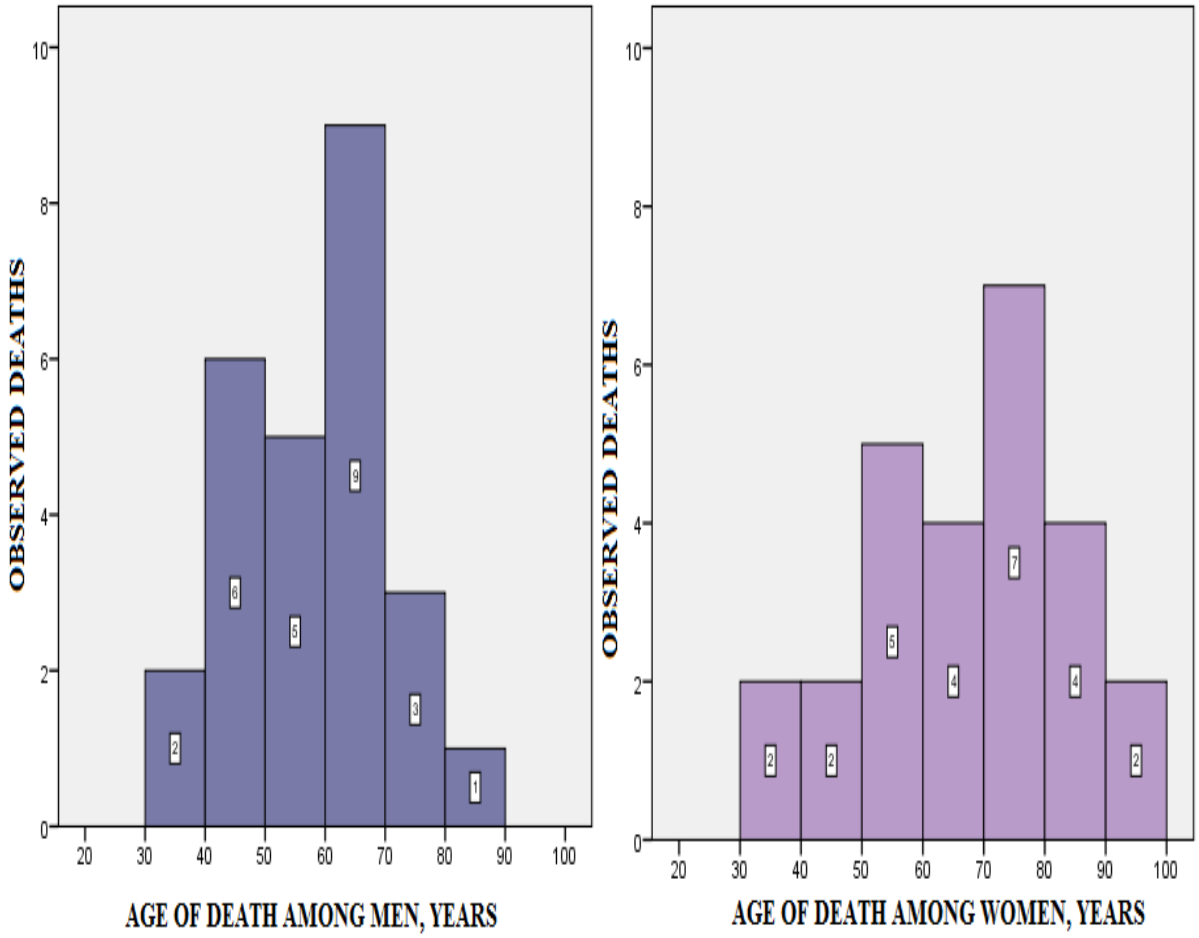
Death causes	Observed deaths	Percent
Women		
Death cause by MI	15	57.7
Death by cerebral infarction	5	19.2
Death by Aortic aneurysm	1	3.9
Possible MI	5	19.2
Total	26	100.0

Women had an average age of death by CVD at 67.2 years. Men had an average age of death by CVD at 57.2 years. Women had higher age of death, than men in all the CVD death categories. Men who died of MI had an average age of death at 56.6 years. Women who died of MI had an average age of death at 62.8 years. For both genders the average age of death by MI was 59.0 years. Persons who died of aortic aneurysm had the highest average death age with 76.3 years.

Table 3.63 Average age of death among categorized CVD deaths.

Death causes	Men	Women	Both genders
Death cause by MI	56.4	62.8	59.0
Death by cerebral infarction	61.0	68.4	67.2
Death by Aortic aneurysm	69.5	90.0	76.3
Possible MI	47.0	74.8	70.2
Total	57.2	67.2	62.2

Figure 3.6 Age of CVD deaths among genders



3.7 Analysis of CVD mortality

Age 0-29 did not have observed CVD deaths. Age 30-59 had higher SMR, than the general population for death by CVD. SMR for death by CVD decreases with increasing age for the age 30-59. Total SMR for death by CVD was significant with 2.1.

Table 3.7 Mortality analysis: CVD both genders (ICD-10 codes I00-I99).

Attained age	Person-years of observation	Observed deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
0-9	461	0	0.0	0	0	0
10-19	3093	0	0.0	0	0	0
20-29	5726	0	0.1	0	0	0
30-39	6265	4	0.5	8.0*	3.0-21.3	64
40-49	7533	8	2.5	3.2*	1.6-6.4	106
50-59	6775	10	7.2	1.4	0.8-2.6	147
Total	29853	22	10.3	2.1*	1.4-3.2	74

***p<0.05**

3.8 Analysis of CVD mortality with consideration of gender and age

The mortality analysis of death by CVD with consideration of gender suggests that both genders have a higher SMR than the general population in age 0-59. SMR is decreasing with increasing age for both genders after 20 years of age. For men the total SMR for CVD death in the age 0-59 was 1.7. For women the total SMR for CVD death in the age 0-59 was significant with 3.6.

Table 3.8 Mortality analysis: CVD with consideration of gender (ICD-10 codes I00-I99)

Attained age	Person-years of observation	Observed Deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
Men						
0-19	1946	0	0.0	0.0	0	0
20-39	5806	2	0.5	4.0	1.0-16.0	34
40-59	6980	11	7.1	1.6	0.9-2.9	158
Total	14732	13	7.6	1.7	1.0-2.9	88
Women						
0-19	1608	0	0.0	0.0	0	0
20-39	6185	2	0.2	10.0*	2.5-40.0	32
40-59	7328	7	2.3	3.0*	1.4-6.3	96
Total	15121	9	2.5	3.6*	1.9-6.9	60

***p<0.05**

3.9 Analysis of mortality by CVD with consideration of periodic intervals

In the age 0-59 both periods had a significant higher SMR than the general populations for death by CVD. SMR is decreasing with increasing age for both genders after 20 years of age.

In period 1992-2005 the total SMR for CVD death in the age 0-59 was 1.9.

Table 3.9 Mortality analysis: CVD 1992-2005 both genders (ICD-10 codes I00-I99).

Attained age	Person-years of observation	Observed deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
0-19	928	0	0.0	0.0	0	0
20-39	5958	3	0.4	7.5*	2.4-23.2	50
40-59	7446	8	5.5	1.5	0.8-3.0	107
Total	14332	11	5.9	1.9*	1.1-3.4	77

***p<0.05**

In period 2006-2010 the total SMR for CVD death in the age 0-59 was significant with 3.0.

Table 3.91 Mortality analysis: CVD 2006-2010 both genders (ICD-10 codes I00-I99).

Attained age	Person-years of observation	Observed deaths	Expected Deaths	SMR	95% CI	Absolute risk per 100000 person years
0-19	2626	0	0.0	0.0	0.0	0
20-39	6030	1	0.3	3.3	0.5-23.4	17
40-59	6866	10	3.4	2.9*	1.6-5.4	146
Total	15522	11	3.7	3.0*	1.7-5.4	71

***p<0.05**

4. DISCUSSION

4.1 Challenges in the study

Challenges in the categorization of the death causes

In the Norwegian somatic health care, ICD-10 was officially in use 1. January 1999. The WHO introduced ICD-10 in 1993 (91). In our study most of the cases from the period 1992 to 1999 were coded with ICD-10. Three of the deaths were coded with ICD-9. This could suggest a difference in the criteria of death coding between our study population and the general population.

According to the ICD-10 manual, all diseases in the circulatory system are categorized with category block I (87, 88, 89). Persons that had the category block I in the main diagnosis, were defined as death by CVD. Five persons with death cause E78.0 pure hypercholesterolemia were also defined as death by CVD. ICD-10 code E78.0 also includes FH (87, 88, 89). Many studies suggest that individuals with FH are at higher relative risk of death by CVD (70, 71).) This was the reason why we assumed that persons with E78.0 died of MI.

Three persons were defined as possible death by CVD. One person had main death cause insulin dependent diabetes mellitus without complications. The other had main death cause, unspecified diabetes mellitus without complications. Type 2 diabetes mellitus is associated with increased risk of CVD (12, 13). The third possible case had main death cause as fall on and from stairs and steps. This case had several other diagnoses. These other diagnosis included instantaneous death, unspecified CVD and unspecified injury. We can assume that this person has had a cardiovascular event, before the fall from the stairs. It is likely that these three cases died of CVD, but it is impossible to claim with scientific knowledge that these cases died of CVD.

Challenges in the categorization of CVD death causes

Some of the ICD-codes that described the death cause were difficult to categorize in the different CVD categorizes. One case died of peripheral vascular disease, unspecified claudicatio intermittens. 60% of individuals with peripheral vascular disease, unspecified claudicatio intermittens die of MI (93, 94). We assumed that this person died of MI, since

claudicatio intermittens affects the legs and death can only occur as a complication of claudicatio intermittens.

The person that died of left ventricular failure was defined as death by MI. Left ventricular failure is a usual symptom of MI (94, 95).

Some death causes were interpreted as possible MI. 2 persons died of unspecified endocarditis valve. According to the Norwegian doctors hand manual is heart failure the mostly common symptom for endocarditis (96). Cerebral embolism is prevalent in 30% of the endocarditis cases (97).

Studies suggest that atrial fibrillation and flutter are important risk factors for myocardial and cerebral infarctions (98, 99). Atrial fibrillation and flutter is assumed to increase the risk of cerebral infarction (100). Some studies suggest that atrial fibrillation and flutter increases the risk of sudden cardiac death by a 1.31 risk ratio (101). It can be interpreted that the case that died of atrial fibrillation and flutter is at equal risk for myocardial and cerebral infarction.

One person with death cause I80.2 had phlebitis and thrombophlebitis of other deep vessels of lower extremities. Major risk factor for pulmonary infarction is deep vein thrombosis in the leg, which emigrates to the lung arteries. This can cause sudden death by preventing blood and oxygen supplement to the lungs (102). One person died of pulmonary embolism without mention of acute cor pulmonale. We assume that these two cases died of pulmonary infarction.

One person died of cardiomegaly. Cardiomegaly is associated with abnormal heart rhythms, heart valve problems, atherosclerotic disease and sometimes chronic diseases such as thyroid disorders (103, 104). Some of the complications of having enlarged heart are sudden death, heart failure and cardiac arrest (104). It is difficult to determine if this person died of MI.

Challenges in the control of risk factors

Many of the factors that could influence the prevalence of death by CVD are not excluded. 15 of the persons who died of CVD had other diagnosis.

Mostly the other diagnosis confirmed the CVD death cause. Other diagnoses that probably influence the prevalence of death by CVD like hypertension, obesity and diabetes mellitus should have been diagnosed as other diagnosis (13, 14, 18).

The diagnosis unspecified diabetes mellitus without complications is associated with a marked increased risk in the development of atherosclerotic disease (12, 13). One person died of chronic ischaemic heart disease at 66 years of age. This person had also diagnosis of unspecified diabetes mellitus without complications. At age 54, one person died of old myocardial infarction. This person had several other diagnoses. One of the diagnoses was unspecified diabetes mellitus without complications. We can assume that these two cases would have had longer life age, if they did not have unspecified diabetes mellitus without complications.

Dementia often disables individuals to function in their daily life by reducing cognitive functions. Some individuals with dementia are not able to have a normal memory, attention and problem solving skills (105, 106). One person died of unspecified chronic ischaemic heart disease. This person had secondary diagnosis unspecified dementia. We can assume that this person has forgotten to have a good adherence to dietary and medical recommendations. If this is correct then we can assume that this person would have had a higher life age.

According to WHO, among patients with chronic illness, approximately 50% do not take medications as prescribed (107). Other long term studies suggest that adherence to statin therapy is low (108). A study analyzed a database with 21393 subjects who received at least one prescription for statins during the period between 1994 and 2003. The adherence to statin therapy reminded low with a with a 50% discontinuation rate in the first year (108).

A study with 336 FH patients examined adherence to the use of medications. A total of 36.6% reported total adherence to the use of cholesterol lowering medication. 64.4% reported some level of none adherence, but only 15% reported that they had quit medical use. The study suggested that patients with FH had overall high levels of adherence to the use of medication (109).

It is unknown if the study population had good adherence to the dietary and medical recommendations. Adherence to dietary and drug advices could have affected the mortality age.

4.2 Methodological consideration

Methodological consideration of person years

We did not have the date when the first 704 persons were included in the FH registry. We estimated for all besides of one case, that they were included in the FH registry in 01.01.1992. This case was born after 01.01.1992. We estimated that this case was included in the FH registry the day after birth. The person years would probably have had other estimates, if we had the accurate datum of the registration of all cases.

This study did not take consideration of censored cases. It can be assumed that some persons have changed their ID-number or that they have emigrated to other countries. It is possible that some persons could have been excluded from the FH registry, before our end point. In the Simon Broome study five cases were censored because of emigration (60). Our study had about four times more individuals than the Simon Brome study. If we can expect to have four times more censored cases than the Simon Broome study, then this study would have had around 20 censored cases. The estimate of person years would have been lower, if the study had taken consideration of censored cases, but still 20 of 4688 is a small fraction.

Methodological limitations in the statistical method

Our study used 95% CI to test if the results were significant. Many other studies use p-value to test significance. Significance by 95% CI and the p-value are estimated from the same test observation. This makes a similarity between the 95% CI and p-value. Usually a significant 95% CI is assumed to give a significance with a p-value <0.05 (90). It is therefore not possible to claim that significant results defined by the 95% CI are more unstable than significant result defined by the p-value (90).

Some of the results from the mortality analysis were not significant. The study samples were probably too small to give significant results for every age group (90).

Standardization facilitates comparisons between populations with distinct gender and age structures (110). The most used statistical methods for standardization are direct standardization and indirect standardization. Each of these standardization methods has limitations. The direct standardization indicates instability, when the populations to be age adjusted are small. Even for small age adjusted populations indirect standardization achieves

precision in the estimates. It is difficult to conduct a valid internal comparison in the study population with indirect standardization (110, 111).

For both standardization methods the main problem is selecting a proper population that is multiplied with the person years (111).

Individuals with FH are in this study compared to the general population. There can be small population groups in the general population who have high prevalence of deaths by none and CVD deaths.

In the general population there are individuals with genetic lipid disorders. Example of these genetic diseases can be LPL mutations that cause primary hypertriglyceridemia (112, 113). Our study population is compared to a general population where it can be population groups that have higher risk for CVD and none CVD mortality, than the general population.

Methodological limitations in the study design

In none placebo controlled studies there is a possibility for confounding (114). Risk factors like diabetes, hypertension and obesity can have influenced our study population and the general population. Risk factors could have influenced these two populations in different ways. This could have given our study misleading results.

About 15000 individuals have FH in Norway (33). In 2010, 4688 individuals were registered in the FH registry. Our study population is not a random sample of a population. It is possible that selection bias has occurred (115).

There are different ways for screening FH. To genetically screen the entire population in a country is not cost effective. The most cost effective way to detect FH is by cascade screening (22). This means to investigate first degree relatives of an already diagnosed FH individual. To diagnose FH, a premature ischemic heart disease history must be present in the case or a close relative (32).

The mortality analysis for CVD mortality in the periods 1992-2005 and 2006-2010 suggest that the period 2006-2010 has a higher total SMR, than the period 1992-2005. In the period 1992-1999 the linked registry had 9 observed deaths. Of these observed deaths, four died of CVD.

Some individuals are possibly more attentive on FH after a mortality case in a close relative. It is possible that persons that had experienced a cardiovascular event in a close relative were interested to investigate if they had FH. This could have given a selection bias where the individuals in the FH registry, were selected after mortality incidences. Individuals could have been diagnosed with FH after CVD death in a close relative that was not registered in the FH registry. This could specially have been prevalent in the beginning of the study period.

We can also assume that persons who have most knowledge about health and are most strict with personal health care, are in the FH registry. These cases experience maybe stronger symptoms of FH than other FH patients.

The estimates from our study would probably have been different if we had excluded some of the confounding and selection bias.

4.3 General discussion

Consideration of the study population

The FH registry is a big study population. It has almost an equal distribution of gender. The birth year of the individuals in the FH registry, suggest that the FH registry has an approximate normal distribution of age. The FH registry has a periodic interval of 19 years. These factors make our study population very similar to the general Norwegian population, but still it is unclear if our results can be generalized to subgroups in the general population.

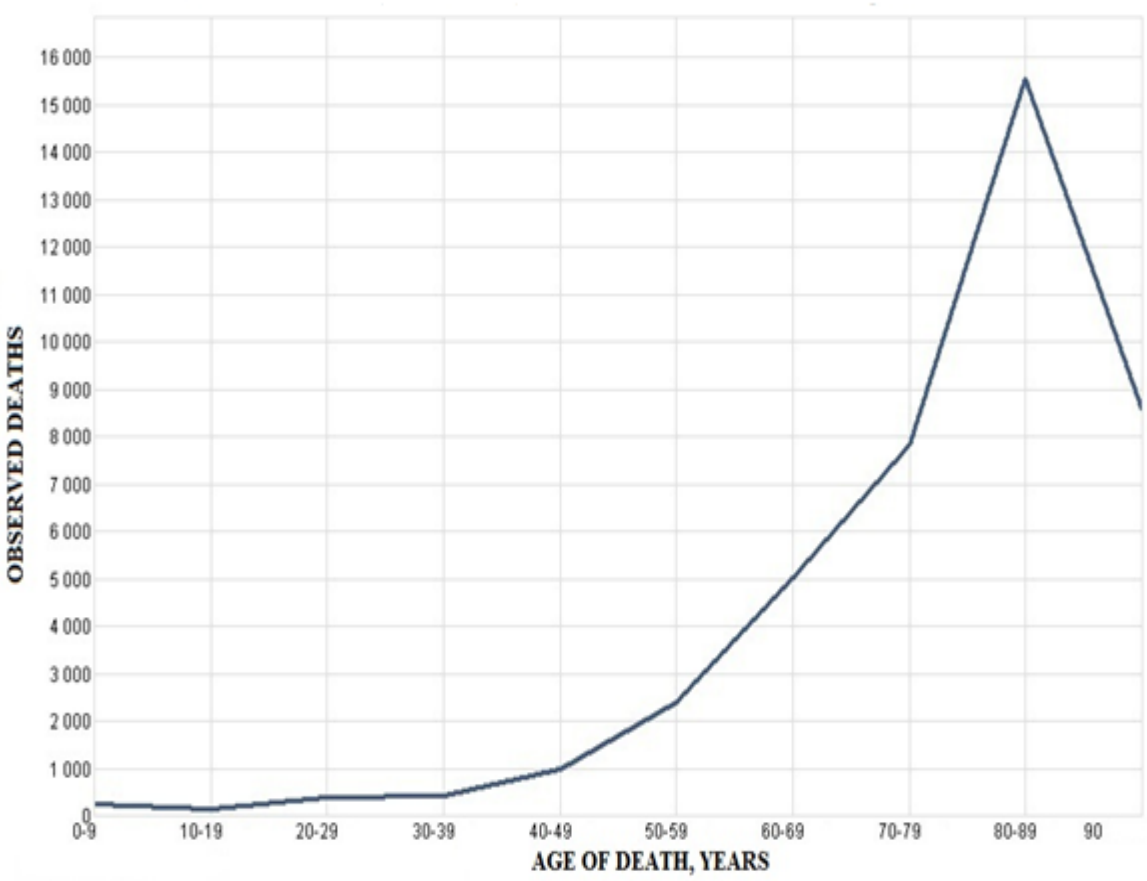
We do not know the socioeconomic status (SES) of each individual. Several studies suggest that people with lower SES have higher prevalence of CVD risk factors, such as obesity, hypertension, diabetes mellitus and hypercholesterolemia (116, 117).

Some studies suggest differences in lipid metabolism between different ethnic groups. It has been suggested that African American women have lower plasma TG and higher HDL-C levels, than Caucasians American women (118, 119). Heritage family study examined the effects of race on plasma lipids and LPL activity. In this study both African American men and women had higher LPL activity and lower hepatic lipase activity than Caucasians Americans (120). This could explain why African American women have an increased clearance of TG from plasma (119).

Consideration of mortality analysis

In 2010, the expected death age in Norway was 83.2 years for women and 78.9 years for men. In the period 1991-1995 the expected age of death was 80.4 years for women and 74.4 years for men (121). It is possible to assume expected death age is approximately the same as average age of death (appendix 3).

Figure 4.0 Prevalence of death in 2010 among the Norwegian population (122).



Our study had an average death age of 61.1 years. If our study population had an average age of death as the general Norwegian population, than it can be assumed that we would have got other results.

The main difference in the average age of death between the FH population and the general population is the prevalence of CVD mortality.

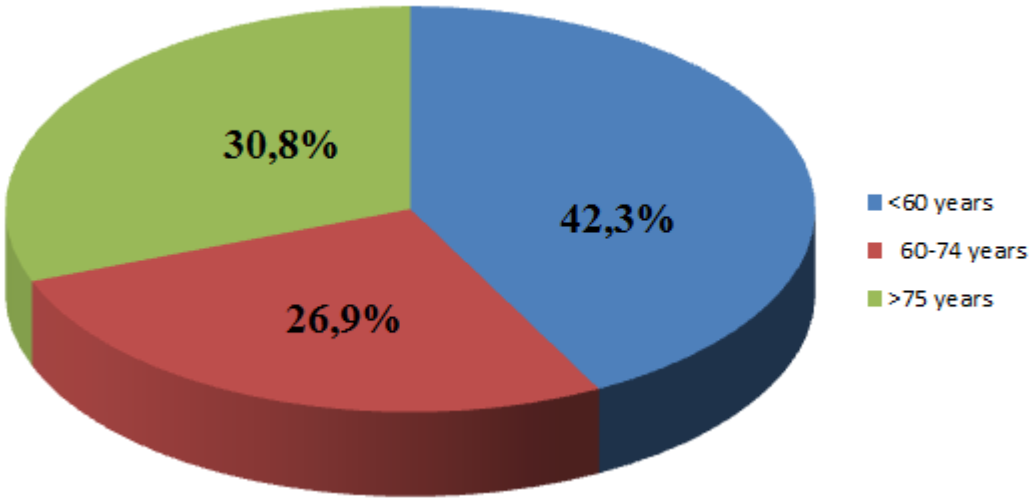
In high income countries 13% of deaths from none communicable diseases are among individuals under 60 years (123). In our study, 42.3% of CVD deaths were before 60 years of age. Total of 22 persons died of CVD before 60 years of age. The first premature CVD deaths

among FH individuals appear in the third and fourth decade of life (76). This could explain why our study population did not have observed CVD deaths in the age 0-29.

Heart disease and stroke deaths rise significantly after 65 years of age. About 75 % of the nearly 5 million patients with heart failure in the United States are older than 65 years (124, 125). In our study 42.3% of the CVD deaths were after 65 years of age.

71% of Norwegian men, who died of CVD in 2006, were over 75 years old. 90% of Norwegian women, who died of CVD in 2006, were over 75 years old (11). In our study 16 persons died of CVD after 75 years of age. This represented 30.8% of CVD deaths.

Figure 4.1 Different age groups as percent of CVD mortality among FH individuals.



Previous studies have shown a significant impact of age on plasma LDL-C levels (126). Plasma LDL-C levels increase progressively from young adulthood to approximately age 60 in men and to age 70 in women. After this plasma LDL-C levels decrease (127). Decrease in LDL-C levels may be partly due to selective survival of individuals with lower cholesterol levels**.** This could indicate that the FH population in the increasing age has had a selective survival (126, 127, 128).

The FH population had about 20 years lower average age of death than the general population. The prevalence of CVD mortality has a different distribution in the FH population compared to the general population. These numbers make it difficult to compare the FH population and the general population with SMR for persons older than 60 years. Results for individuals older than 60 years could be misleading.

4.4 Principal findings

One person died of mitochondrial myopathy. Some studies suggest that therapy with statins can induce lower levels of coenzyme Q10. Coenzyme Q10 facilitates electron transfer in the generation of adenosine triphosphate (ATP) (125). Coenzyme Q10 is important in the mitochondrial bioenergy transfer. An important precursor for coenzyme Q10 is mevolonic acid. Statins inhibit production of mevolonic acid. It is assumed that statin therapy can induce myopathies through coenzyme Q10 deficiency (129).

The individuals in our study have got modern treatment with lipid lowering drugs and dietary advices, but still the prevalence of CVD deaths is higher among FH individuals than the general population.

37% of the general Norwegian population died of CVD in 2010 (130). In our study 46% died of CVD. This could be an indication that individuals with FH have a higher prevalence of death by CVD, than the general population.

Before 60 years of age, men are more prone of death by CVD than women (11, 76). This study also indicates this hypothesis. For men the average age of death by CVD was 57.2 years. For women it was 67.2 years.

Studies suggest that for individuals with FH, the relative risk for death by CVD is at its highest at younger age (60). The relative risk decreases with increasing age (60). This study suggests that SMR decreases with increasing age for CVD deaths in age 29-59. Our study did not have any observed CVD deaths for persons who are younger than 29 years.

71.2% of CVD mortality was by MI. MI counted 32.7% of total mortality. In 1994 among the Norwegian population, 20.5% of women and 26.8% of men died of MI (79). This suggests that death by MI is more prevalent in FH patients, than the general population.

22 men and 15 women died of MI. The average age of death for men by MI was 56.4 years. For women these estimates were 62.8 years. These estimates suggest that men have a higher prevalence and lower age of death by MI than women.

Three persons died of aortic aneurysm. Six persons died of cerebral infarction. Six persons were defined as possible MI. Study samples for these death causes are small. Small study samples make it difficult to suggest gender differences for these death causes. It is difficult to

claim differences between our study population and the general population for these death causes.

This study suggests that individuals with FH have higher SMR of death by CVD, than the general population at age 0-59. Other studies suggest that individuals with FH are at higher relative risk of death by CVD also after 60 years of age (60).

Clinical relevance

Modern dietary and drug interventions are available for treatment of FH, but still the prevalence of CVD deaths is higher among FH individuals than the general population.

A study investigated if patients with FH had been adequately treated with lipid lowering drugs (131). A questionnaire was sent to 2611 subjects who had a molecular genetic diagnosis of FH or familial defective apoB-100. Blood sample with lipid measurements were obtained. 956 subjects participated. The average age for starting lipid lowering therapy was 33.4 years. Among those below 18 years of age, only 20.4% were on lipid lowering drugs. 89.1% of those aged 18 and above were on lipid lowering drugs. The average levels of total cholesterol were 5.7 mmol/l. The average levels of LDL-C were 3.9 mmol/l. 29.0% of those on lipid lowering drugs had levels of LDL-C below 3.0 mmol/l. 47.3% of the subjects were considered as being adequately treated (131).

It seems that not all FH patients are treated with lipid lowering drugs. It is also possible that too many FH individuals have begun lipid lowering treatment at a late age. It can therefore be assumed that individuals with FH have been exposed for high cholesterol levels.

European guidelines for the management of dyslipidaemia suggest that FH patients are a high risk group for CVD (132). These guidelines suggest that for heterozygote FH high dose statin is recommended. If needed high dose statin can be in combination with cholesterol absorption inhibitors or bile acid sequestrants. Treatment is aimed at reaching LDL-C levels that are below 2.5 mmol/l (132). It is possible that adherence to the European guidelines for the management of dyslipidaemias can give better mortality prognosis for FH patients.

The use of clinical diagnostic criteria to diagnose FH identifies only approximately 50% of FH patients (133). Molecular genetic testing is an efficient tool to diagnose patients. A study suggested that reductions in total serum cholesterol by 18.4% and 25.3% LDL- C were

observed 6 months after genetic testing among adults with FH mutations. These FH mutation carriers were not on lipid lowering treatment before the genetic testing (133).

4.5 Future perspective

There are few studies on the relationship between FH and mortality. There is need for several studies to scientifically claim the impact from this study.

Future studies could investigate if FH individuals that have got modern treatment from 18 years or younger are at increased risk of premature CVD. It would be very interesting to investigate if these individuals that have got treatment at a young age are less prone for premature CVD death than FH individuals that have got FH treatment late in life.

Studies have investigated differences in prevalence of risk factors among different age groups of FH individuals (134). It would have been interesting to investigate if these risk factors like high cholesterol levels would have been less prevalent if FH individuals were treated with higher doses of lipid lowering drugs.

It would be interesting to compare the individuals that have been diagnosed in the FH registry in the period 1992-1995 with the general population for malignant diseases. This could give further knowledge if long term FH treatment has potential side effects.

4. CONCLUSION

a. Individuals with FH have significantly lower total SMR than the general population for death by cancer and none-CVD death in the age 0-59.
b. Individuals with FH have higher death prevalence by CVD, than the general population.
c. The main death cause by CVD is MI.
d. Women had a 10 years higher average age of death by CVD than men.
e. This study suggests that both men and women with FH at the age 0-59 have higher SMR by CVD, than the general population.

Individuals with FH have a lower average age of death than the general population. If we could assume that individuals with FH would have same age of death as the general population, then it would be possible to assume that individuals with FH would have had a higher SMR for death by CVD also after 60 years of age.

Modern dietary and drug interventions are available for treatment of FH, but still the prevalence of CVD deaths is higher among FH individuals than the general population. There is a need for more studies to investigate how modern dietary and drug treatment has affected the prevalence of CVD deaths among individuals with FH.

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7. APPENDIX

APPENDIX 1: APPROVAL FROM THE REGIONAL ETHIC COMMITTEE

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Katrine Ore	22845517	23.09.2011	2011/1343/REK sør-øst B
			Deres dato:	**Deres referanse:**
			15.06.2011	

Vår referanse må oppgis ved alle henvendelser

Førsteamanuensis Kjetil Retterstøl

Universitetet i Oslo
Avdeling for ernæringsvitenskap

2011/1343b Sykelighet og medikamentbruk hos personer med familiær hyperkolesterolemi

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk i møtet 17.08.2011.

Forskningsansvarlig: Oslo universitetssykehus HF ved øverste ledelse
Prosjektleder: Kjetil Retterstøl

Prosjektomtale (revidert av REK):
Prosjektet er en registerstudie med tre overordnede mål. En ønsker å kartlegge behandling, sykelighet og dødelighet for personer med familiær hyperkolesterolemi. Prosjektet vil også kunne gi økt kunnskap om den helsemessige betydningen av høyt kolesterol og kartlegge helseeffekter av langtids kolesterolsenkende behandling blant annet i forhold til graviditet, bruk av slike medikamenter på barn og i forhold til utvikling av kreft. Det skal benyttes allerede registrerte data på pasientgruppen i et etablert helseregister ved medisinsk genetisk laboratorium ved Oslo Universitetssykehus, Rikshospitalet. I dag er det i underkant av 5000 pasienter registrert med opplysninger om diagnosekriterier, lipidprofil, eksisterende hjerte- og karsykdom, høyde og vekt, tidspunkt for diagnose og kardiovaskulær sykehistorie samt mutasjonestype. Man ønsker å koble mot et begrenset utvalg av opplysninger i en rekke av de sentrale helseregistrene; Kreftregisteret, Dødsårsaksregisteret, NPR, Reseptregisteret, Medisinsk fødselsregister og Nasjonalt kvalitetsregister (hjerte- og karregisteret). Kobling skal skje ved Folkehelseinstituttet, Kreftregisteret og Helsedirektoratet i henhold til beskrivelse i protokollen s. 8. Forskerne vil få aggregerte og for dem anonyme data der ingen data med n ‹10 vil bli analysert.

Forskningsetisk vurdering
Prosjektet skal vurderes av REK fordi det skal brukes personidentifiserbare data fra pasientregisteret for personer med familiær kolesterolemi ved OUS som skal kobles mot opplysninger ved de sentrale helseregistrene.

Alle pasientene i pasientregisteret ved OUS har i følge protokollen samtykket i å stå i registeret. Det er fra prosjektleders side lagt opp til en form for passivt samtykke slik at deltakerne tilskrives med informasjon om prosjektet og gis mulighet til å reservere seg.

Dette er ikke et samtykke etter helseforskningsloven § 13 hovedregel om samtykke, som krever et informert, frivillig, uttrykkelig og dokumenterbart samtykke, jf. andre ledd. Komiteen må derfor vurdere hvorvidt unntaket fra kravet til samtykke i helseforskningsloven § 35 er oppfylt. Adgang til bruk av helseopplysninger som er samlet inn i helsetjenesten til forskning må være av vesentlig interesse for samfunnet og hensynet til deltakernes velferd og integritet må være ivaretatt. Prosjektet er etter komiteens vurdering av stor interesse for samfunnet fordi det vil kunne gi viktig dokumentasjon av hvordan forebyggende tiltak virker på en gruppe pasienter med særlig høy hjerte-karsykdoms risiko. Det er mange deltakere og det er viktig å få god representasjon for å få svar på forskningsspørsmålene. Hensynet til deltakerne synes vel ivaretatt med hensyn til behandlingen av opplysningene som innhentes. Komiteen gir på denne bakgrunn fritak fra taushetsplikten.

Komiteen mener det er spesielt viktig ved denne formen for registerstudier at en ikke tilskriver døde med informasjon om studien fordi dette kan virke støtende på pårørende. Det stilles derfor som krav at data i pasientregisteret sammenstilles med Dødssårsaksregisteret før det sendes informasjon med reservasjonsadgang til de registrerte.

Vedtak
Komiteen godkjenner at prosjektet gjennomføres under forutsetning av at ovennevnte vilkår oppfylles.

Fordi det skal sammenstilles (kobles) opplysninger fra forskriftsregulerte helseregistre med et lokalt pasientregister ved Medisinsk Genetisk Laboratorium, OUS, Rikshospitalet, kreves det forhåndsgodkjenning og dispensasjon fra taushetsplikten fra REK i henhold til helseforskningsloven § 33 jf. § 9 for å kunne gjennomføre denne sammenstillingen og gi prosjektet det nødvendige behandlingsgrunnlaget for behandling av personopplysninger.

Komiteen godkjenner dispensasjon fra taushetsplikten for kobling av forskningsdata med Dødsårsaksregisteret, Kreftregisteret, Norsk pasientregister og Reseptregisteret i prosjektet med hjemmel i helseforskningsloven § 35. Dispensasjonen fra taushetsplikten gjelder kun for de opplysningene som er relevant for undersøkelsen. Dispensasjonen gjelder for prosjektleder førsteamanuensis dr. med. Kjetil Retterstøl, professor dr. med. Per Ole Iversen, dr. philos. Marit Veierød, seksjonsoverlege professor dr. med. Leiv Ose og Trond Leren.

Enhver publikasjon basert på studien må skje i en slik form at enkeltpersoner ikke kan gjenkjennes. Dispensasjonen fra taushetsplikten gjelder også institusjonens databehandlingsansvarlig.

Registerkoblingene i prosjektet kan ikke deles med andre forskningsgrupper for andre forskningsspørsmål enn beskrevet i dette prosjektets forskningsprotokoll.

Dispensasjonen fra taushetsplikten gjelder tidsrommet fra dags dato til prosjektslutt 01.01.2016. Personidentifiserbare data slettes straks det ikke lenger er behov for dem og senest ved prosjektets avslutning.

Det er prosjektleders ansvar å påse at taushetsplikten overholdes i henhold til helseforskningsloven § 7 og forvaltningsloven § 13 d.

Godkjenningen er for øvrig gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, og de bestemmelser som følger av helseforskningsloven med forskrifter.

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

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

Godkjenningen gjelder til 01.01.2016.

Prosjektet skal sende sluttmelding på eget skjema, se helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

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

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Stein Opjordsmoen Ilner (sign.)
professor dr. med.
komiteleder

Katrine Ore
Komitésekretær/Rådgiver

APPENDIX 2: FORMULA FOR INTERNAL REGISTRATION. INTERNAL CONTROLL AND SETTLING OF RESEARCH RESPONSIBILITY AT OSLO UNIVERSITY HOSPITAL.

A. INFORMASJON OM SØKER OG STUDIENS NAVN OG FORMÅL

1 INFORMASJON OM SØKEREN (For studier som OUS er forskningsansvarlig for, må prosjektleder ha et formelt forhold til OUS, dvs. være ansatt eller via avtale være under instruksjonsmyndighet av OUS.)
Deltagelse i ekstern studie: Før opp både internt og eksternt ansvarlig.

Navn og stilling:	Avdeling hvor prosjektet gjennomføres:
Kjetil Retterstøl	Avdeling for ernæringsvitenskap/Det medisinske fakultetet ved UiO Klinikk:
Telefonnummer:	E-postadresse:
90098393	kjetil.retterstøl@medisin.uio.no

2 PROSJEKTETS NAVN / TITTEL

Hvordan har mortaliteten blant mennesker med familiær hyperkolesterolemi(FH) endret seg i perioden 1995 til 2010?

3 BESKRIV FORMÅLET (HOVEDMÅL OG DELMÅL VED PROSJEKTET)

Gjør en systematisk kartlegging av utviklingen av mortalitet hos personer med familiær hyperkolesterolemi(FH) i perioden 1992 til 2010. Vi håper på å kartlegge utviklingen av levealder ved denne perioden.

Gjør en systematisk kartlegging av utviklingen av mortalitet hos personer med familiær hyperkolesterolemi(FH) i perioden 2000 til 2010 med hensyn til dødsårsak, kjønn og alder. De dødsårsakene vi spesielt ønsker å se nærmere på, er dødsfall ved hjerteinfarkt, hjerneslag og aortaaneurisme. Dødsårsakene blir definert ut fra ICD-10 kriteriene.

4 PROSJEKTBESKRIVELSE, kort (bakgrunn, metoder, anvendte metoder, evt. preliminære resultater).
Praktisk info: Hvilke pasienter/personer (antall) skal inkluderes, inklusjonsperiode (spesielt rekrutteringstid der avdelingen er involvert), fra hvor, på hvilken måte, av hvem, behov for innsats fra OUS-ansatte osv.

Bakgrunn:

Familiær hyperkolesterolemi (FH) karakteriseres av høye plasmaverdier av totalkolesterol og LDL(low density lipoprotein). Ubehandlet medfører familiær hyperkolesterolemi(FH) til økt sirkulasjon av totalkolesterol og LDL(low density lipoprotein) i plasma. Dette gir økt risiko for hjerte- og karsykdommer. Før 50 års alder angis 50 % av menn, som er ubehandlet for heterozygot familiær hyperkolesterolemi(FH) å få hjerte- og karsykdom. Før 60 års alder angis 50 % av kvinner, som er ubehandlet for heterozygot familiær hyperkolesterolemi(FH) å få hjerte- og karsykdom. Levealderen antas å være redusert med 20–30 år for disse to gruppene. Hjerteinfarkt er den vanligste dødsårsaken i Norge, mens hjerneslag er den tredje hyppigste dødsårsaken

Metode: Personnummer på pasienter fra familiær hyperkolesterolemi registeret vil bli koblet opp mot data i Dødsårsaksregisteret.

Utvalg:I Norge er det registret ca. 4800 personer med familiær hyperkolesterolemi(FH). Disse personene er registrerte i et familiær hyperkolesterolemi register, som strekker seg over 15 år tilbake i tid.

Forskerinitiert prosjekt	Rent OUS-prosjekt	Multisenterstudie ledet av OUS	Multisenterstudie ledet eksternt	Oppdragsforskning
☒ Ja ☐ Nei	☐ Ja ☒ Nei	☐ Ja ☒ Nei	☐ Ja ☒ Nei	☐ Ja ☒ Nei Hvis Ja se pkt. B xi)

5 EMNEORD (max 5) FOR PROSJEKTET, FRA HEALTH RESEARCH CLASSIFICATION SYSTEM

Familiær hyperkolesterolemi (FH), mortalitet, dødsårsak, alder, utvikling

6 PROSJEKTPERIODE
(fra start rekruttering til og med publisering og eventuelt oppbevaring av opplysninger og / eller biologisk materiale deretter)

Oppstart:	Avslutning:
22.08.2011	15.06.2012

Del B avklarer hva som videre skal fylles ut
Selv om prosjektet er del av tematisk konsesjon eller kvalitetsregister må internkontroll og forankring av forskningsansvar, samt ekstern godkjenning gjennomføres

B. AVKLARING PÅ BEHOV FOR FORMALISERING

i) Er prosjektet intern kvalitetssikring? (jmf. § 26 i Helsepersonelloven)

☐ **Ja** ☒ **Nei**

Dersom Ja, fyll kun ut del C og pkt. E 14

ii) Er prosjektet kvalitetsstudie?

☒ **Ja** ☐ **Nei**

Dersom Ja, skjemaet fylles ut, men kun intern prosess er nødvendig. Personvernombudets tilrådning gir den formelle godkjenning

iii) Er prosjektet forskning?

☒ **Ja** ☐ **Nei**

Fyll ut relevante deler av skjemaet. Internkontroll og forankring av forskningsansvaret, samt ekstern godkjenning er nødvendig

iv) Brukes personopplysninger, inkludert kodede?

☒ Ja ☐ Nei

Dersom **Ja**, fyll ut **del C** i dette skjema

v) Er prosjektet klinisk forsøk?
☐ Ja ☒ Nei

Vil forsøkpersoner prospektivt bli inkludert til én behandlingsgruppe eller til sammenlignede grupper for å undersøke effekten av helserelaterte og/eller legemiddelrelaterte endepunkt?
(Gjelder alle randomiseringsstudier)

☐ Ja ☒ Nei

Dersom **Ja**, må prosjektet registreres i Clinicaltrials.gov Protocol Registration System.
Ved forskerinitierte prosjekt registrerer prosjektleder, kontakt Stab forskning, innovasjon og utdanning for tilgang (e-post: post.forskning@ous-hf.no).
Ved oppdragsforskning vil vanligvis sponsor registrere

Er studien en observasjonsstudie?
☐ Ja ☒ Nei

I økende grad vil tidsskriftene også kreve at observasjonsstudier registreres i i Clinicaltrials.gov Protocol Registration System

vi) Innebærer prosjektet klinisk utprøving av legemidler til mennesker, inkludert sammenligning av eksisterende behandlingsregimer?

☐ Ja ☒ Nei

Dersom **Ja**, må søknad til Statens legemiddelverk sendes etter intern godkjenning er gitt (hvis ikke sponsor/oppdragsgiver gjør det)
Legemiddelstudier krever også egen forsikring

Kontaktopplysninger på sponsor:
Navn:

Adresse:

vii) Ønskes rådgivning i Good Clinical Practice (GCP) eller monitorering?

☐ Ja ☒ Nei

Krysses det av for **Ja** her vil din forespørsel vurderes og du vil motta en tilbakemelding på dette

(Det er pålagt å følge retningslinjene for Good Clinical Practice ved legemiddelstudier)

viii) Omfatter prosjektet klinisk utprøving av medisinsk utstyr?

☐ Ja ☒ Nei

Dersom **Ja**, må melding sendes til Helsedirektoratet

Involverer prosjektet utprøving av medisinskteknisk utstyr?

☐ Ja ☒ Nei

Dersom **Ja**, må Medisinskteknisk avdeling kontaktes før utstyret tas i bruk

ix) Brukes biologisk materiale, inkludert tilleggsprøver og tilleggsanalyser?
☐ Ja ☒ Nei

Dersom **Ja**, fyll ut **del D** i dette skjema

x) Omfatter prosjektet også dyreforsøk?

☐ Ja ☒ Nei

Dersom **Ja**, må kopi av godkjenning ved ansvarshavende for forsøksdyravdelingen fremlegges

xi) Skal det inngås kontrakter med eksterne enheter i forbindelse med prosjektet?
☒ Ja ☐ Nei

Dersom **Ja**, og den eksterne enhet er en industriell enhet, må Inven2 kontaktes (post@inven2.com)
Dersom **Ja** og den eksterne enhet er en forskningsinstitusjon, må Seksjon for Forskningsadministrasjon kontaktes
(e-post: geir.gogstad@ous-hf.no)

C. MELDING OM BRUK AV PERSONOPPLYSNINGER

(for forskningsstudier, kvalitetssikringsstudier, kvalitetssikring og annen aktivitet som medfører behandling/bruk av personopplysninger, inkl. avidentifiserte/kodede opplysninger)

7 RETTSLIG GRUNNLAG FOR BEHANDLING AV PERSONOPPLYSNINGENE[1]

7.1 Samtykke

Skal det innhentes skriftlig samtykke fra den registrerte? ☐ Ja ☒ Nei

Hvis nei, begrunn hvorfor: Personene som er registrete i dødsårsaksregisteret er døde. Alle som er registrert i pasientregisteret for FH har tidligere avgitt skriftlig samtykke for dette som er arkibert på Medisinsk Genetisk Avdeling.

Skal det innhentes skriftlig samtykke fra andre enn den registrerte? ☐ Ja ☒ Nei

Hvis ja, av hvem?

Hvis barn inkluderes, angi alder

Skal det søkes om unntak fra taushetsplikt? ☐ Ja ☒ Nei

ELLER

7.2 Intern kvalitetssikring av pasientbehandling, jmf Helsepersonelloven § 26

☐ Ja, prosjektet oppfyller Helsepersonelloven § 26

Opplysningene må være slettet eller anonymisert før eventuell publisering av resultater. Må publiseres som kvalitetssikring, ikke som forskning.
Det kreves ikke samtykke. Personopplysningsloven § 33, 4. ledd gir unntak for konsesjon, men krever melding.
Det er ikke krav til samtykke, men pasienter som har reservert seg mot slik bruk av opplysningene skal respekteres.

ELLER

7.3 Annet som hjemler melding, angi årsak/hjemmel:

8 SLETTING/ANONYMISERING

Angi tidspunkt for sletting/anonymisering av data: 2015

Beskriv hvordan data vil bli slettet/anonymisert: Papir makuleres og datafiler slettes

9 DETALJER OM PROSJEKTETS INFORMASJONSBEHANDLING

Følgende ansvar gjelder ifm innsamling, registrering og bruk av personopplysninger:

- opplysningene skal være tilstrekkelige og relevante i forhold til formålet med den planlagte databehandling
- opplysningene skal være korrekte og oppdaterte

9.1 Type personopplysninger databehandlingen / prosjektet skal omfatte:

9.1.1
Hvis det benyttes kobling mot forskriftsregulerte registre (som for eksempel fødselsregister, kreftregister, dødsårsaksregister, eller interne konsesjonsbelagte registre) angi hvilke registre: Dødsårsaksregister

Angi totalt antall inkluderte: 4800
Ved multisenterstudie, hvor mange inkluderte fra OUS:

9.1.2 Ikke-sensitive personopplysninger

Identifikasjonsopplysninger
- ☒ Navn, adresse, fødselsdato
- ☒ Fødselsnummer (11 siffer)
- ☐ Fingeravtrykk, iris
- ☐ Annet:

Opplysninger om tredjepersoner (familie/slektning)
- ☐ Navn, adresse, fødselsdato
- ☐ Fødselsnummer (11 siffer)
- ☐ Annet:

Adferdsopplysninger
- ☐ Loggføring av adferd
- ☐ Preferanser (ønsker, behov og lignende)
- ☐ Annet:

9.1.3 Sensitive personopplysninger (jf. personopplysningsloven § 2 nr. 8)

Prosjektet omfatter opplysninger om
- ☐ rasemessig eller etnisk bakgrunn, eller politisk, filosofisk eller religiøs oppfatning
- ☐ at en person har vært mistenkt, siktet, tiltalt eller dømt for en straffbar handling
- ☒ helseforhold
- ☐ seksuelle forhold
- ☐ fagforeningstilhørighet

Presiser nærmere: Personer med diagnostisert familiær hyperkolesterolemi(FH) blir sammenlignet i Dødsårsksregisteret for å se utviklingen i forhold til mortalitet.

Behandles spesielt inngripende opplysninger, i så fall hvilke?

9.2 Utvalg

Informasjonsbehandlingen omfatter opplysninger om (beskriv også eventuell kontrollgruppe):

☐ Ansatte i egen virksomhet ☐ Elever/studenter/ barnehagebarn ☒ Pasienter ved OUS ☐ Tilfeldig utvalgte

☐ Adgangskontrollerte ☐ Medlemmer ☐ Pårørende ☐ Seleksjonsutvalgte

☐ Friske frivillige ☐ Pasienter ved andre sykehus/institusjoner ☒ Andre

Dersom det skal gis godtgjørelse, beskriv nærmere: I Norge er det registret ca. 4800 personer med familiær hyperkolesterolemi(FH). Disse personene er registrerte i et familiær hyperkolesterolemi register, som strekker seg over 15 år tilbake i tid.

9.3 Innsamling av opplysningene

Hvordan samles personopplysningene inn?

☐ Manuelt ☐ Elektronisk (bilde og tekst) ☐ Videoopptak ☐ Lydopptak ☒ Annet (beskriv hvordan): Familiær hyperkolesterolemi(FH) og Dødsårsaksregisteret

Hvor innhentes personopplysningene fra?
☐ Fra den registrerte selv
☒ Annet (beskriv hvor fra): Familiær hyperkolesterolemi (FH) og Dødsårsaksregisteret

Hvordan oppnås kontakt med de som skal inkluderes?

Hvis innsamling av personopplysninger skal gjøres fra andre virksomheter, hvordan skal dette gjennomføres?

9.4 Utlevering av opplysningene

Blir personopplysningene gjort tilgjengelige/utlevert til andre virksomheter? ☐ Ja ☒ Nei

Dersom ja:

Oppgi mottakeres navn og adresse:

Er virksomheten innenfor EU/EØS? ☐ Ja ☐ Nei

Vil den eksterne virksomheten brukes som ressurs/laboratorium/annet for denne studien? ☐ Ja ☐ Nei

Vil mottakeren ha eget formål/studie? ☐ Ja ☐ Nei

Hva blir overført?

☐ Informasjon med navn, fødselsnummer eller annet som entydig angir det enkelte individ

☐ Anonymisert informasjon

☐ Avidentifisert informasjon. Forklar i så fall hvordan kryssreferanseliste beskyttes dersom dette ikke er likt som i pkt. 9.6:

Hvordan oversendes informasjonen?

☐ Personlig overlevering

☐ CD sendt med rekommandert post

☐ Registreres på sikret web-side hos mottaker

☐ Legges ut på sikret område for nedlasting av mottaker

☐ Annet, nærmere beskrivelse:

9.5 Lagring og behandling av opplysninger

Hvordan lagres opplysningene?

- ☐ Forskningsserver på Ullevål
- ☐ Kvalitetssikringsserver på Ullevål
- ☐ Forskningsserver på Aker
- ☐ Forskningsserver på Rikshospitalet
  - ☒ O:Forskning
  - ☐ Forskernett
  - ☐ MEDinsight
- ☐ På papir. Forklar hvordan dette sikres mot uvedkommende:
- ☐ På video, tape eller annet opptak. Beskriv hvordan dette er sikret og om personen kan identifiseres:
- ☐ Annet (for eksempel andre virksomheters nettverk). Forklar:

9.6 Gjenfinning av opplysningene

Hvordan gjenfinnes opplysningene? (Bruk av direkte identifisering som fødselsnummer og navn skal forsøkes unngått)

- ☐ Opplysningene lagres med navn, fødselsnummer eller annet som entydig angir det enkelte individ
- ☒ Opplysningene lagres avidentifisert (ved bruk av krysslister, kodelister, løpenummer eller lignende)

Hvordan er krysslister/kodelister beskyttet/lagret? Forklar: På papir på innelåst kontor

D. BRUK AV HUMANT BIOLOGISK MATERIALE

10 BIOBANK

Medfører prosjektet bruk av humant, biologisk materiale? ☐ Ja ☒ Nei

Dersom ja:

Benyttes en allerede eksisterende biobank? ☐ Ja ☐ Nei

Hvis **ja**, angi
☐ tematisk forskningsbiobank (basert på bredt samtykke) *
☐ spesifikk forskningsbiobank (basert på samtykke til et spesifikt prosjekt)
☐ generell biobank (legemiddelselskap som ansvarshavende)
☐ diagnostisk biobank
☐ behandlingsbiobank

* Om prosjektet skal benytte seg av materiale fra en tematisk forskningsbiobank må det innhentes godkjenning fra prosjektleder av denne (se pkt. E 13)

Navn på biobank:

Biobankregisternr.:

Opprettes forskningsbiobanken som en ny spesifikk biobank? ☐ Ja ☐ Nei

Opprettes forskningsbiobanken som en ny tematisk biobank? ☐ Ja ☐ Nei

Ansvarshavende person for forskningsprosjektets biobank
(Helseforskningsloven § 26):

Forskningsbiobankens navn:

Forskningsbiobankens innhold (vev, blod og lignende) og antall inkluderte:

Gjøres genetiske undersøkelser som har diagnostiske, prediktive eller behandlingsmessige konsekvenser for deltakeren? ☐ Ja ☐ Nei

Er genetiske opplysninger tenkt tilbakeført til deltakeren? ☐ Ja ☐ Nei

Hvis **Ja** se pkt. E 12, må være godkjent hos avd. for Medisinsk genetikk

Angi planlagt innsamlingsperiode og tidspunkt for opphør av biobanken:

Hva skjer med biobankmaterialet:
☐ Materialet oppbevares etter prosjektslutt, til år:
☐ Materialet destrueres fortløpende i prosjektet
☐ Materialet destrueres ved prosjektavslutning
☐ Materialet føres tilbake til eksisterende biobank

☐ Materialet overføres til annen biobank Hvilken:

☐ Skal biobankmateriale overføres til annen institusjon? Hvilken:
☐ Skal biobankmateriale overføres til institusjon utenfor EU/EØS? Hvilken:

Annet:

11 RETTSLIG GRUNNLAG FOR BEHANDLING AV BIOBANKMATERIALE[2]

Skal det innhentes skriftlig samtykke fra den inkluderte?
☐ Ja ☐ Nei
Hvis nei, begrunn hvorfor ikke:

Skal det innhentes skriftlig samtykke fra andre enn den inkluderte?
☐ Ja ☐ Nei
Hvis ja, fra hvem?
Hvis barn inkluderes, angi alder:

Skal det søkes om unntak fra samtykke?
☐ Ja ☐ Nei

E. LOKAL FORANKRING

12 SAMARBEID FRA ANDRE AVDELINGER (interne/eksterne), BIOLOGISK MATERIALE OG JOURNALINFORMASJON Dersom annen avdeling enn initierende forutsettes å bruke ressurser, må avdelingsleder (N3-nivå) bekrefte at studien kan gjennomføres. Dette gjelder slik som å sende ut invitasjoner til deltagelse, ha oversikt over hvem som er inkludert, prøvetaking, oppslag i journal for innhenting av opplysninger og tid for samtaler/intervju. Både prøvetaking og intervjuer griper inn i avdelingens rutiner og ansvar, og må være godtatt.

Type samarbeid fra angitt avdeling	Type og mengde biologisk materiale	Type journalinformasjon	Signatur avdelingsleder (elektronisk sendt fra vedkommendes e-post er tilstrekkelig)
Bruk av pasientregisteropplysninger fra Medisinsk Genetisk Laboratorium		**Pasientregisteropplysninger**	
Bruk av kontorplass og konsultative ressurser fra Avdeling for forebyggende medisin, Lipidklinikken			

13 VED BRUK AV EKSISTERENDE TEMATISK BIOBANK / REGISTER SKAL DET FORELIGGE GODKJENNING FRA PROSJEKTLEDER AV DENNE

Prosjektleder av tematisk biobank / register:

Dato:

Sykehusets styrende dokumenter for forskning er lest:

Sign. prosjektleder av tematisk biobank / register
(elektronisk sendt fra vedkommendes e-post er tilstrekkelig)

14 PROSJEKTLEDER, AVDELINGSLEDER OG FORSKNINGSLEDER I KLINIKKEN

Prosjektleder	**Avdelingsleder (N3-nivå)**	**Forskningsleder i klinikken** (ikke nødvendig ved kvalitetssikring)
Dato:	Godkjent dato:	Godkjent dato:
Sykehusets styrende dokumenter for forskning er lest :		
Sign. prosjektleder (elektronisk sendt fra vedkommendes e-post er tilstrekkelig)	Sign. avdelingsleder (elektronisk sendt fra vedkommendes e-post er tilstrekkelig)	Sign. forskningsleder (elektronisk sendt fra vedkommendes e-post er tilstrekkelig)
Styrende dokumenter for forskning og kvalitetssikring finnes i eHåndboken	**Avdelingsleder vurderer:** • Ønsker avdelingen å delta med sine pasienter? • Etiske vurderinger ved gjennomføring • Har avdelingen ressurser/ pasienter/medarbeidere nok? • Er økonomien tilfredsstillende? • Er oppdraget medisinsk interessant? • Har studien adekvat veiledning?	**Forskningsleder vurderer:** • Er oppdraget medisinsk interessant? • Etiske vurderinger ved gjennomføring • Er det pasientgrunnlag å avse? • Medfører gjennomføring noen former for interessekonflikter? • Er det faglige opplegget tilfredsstillende? • Er den faglige rådgivingen tilfredsstillende? • Er statistiker/epidemiolog kontaktet?

Utfylt skjema sendes til:
godkjenning@rikshospitalet.no

Vedlegg – kryss av:
☒ PROTOKOLL
☒ PASIENTINFORMASJON / SAMTYKKEERKLÆRING
☐ SPØRRESKJEMA / INTERVJUGUIDE
☐ VED LEGEMIDDELSTUDIE – LEGG OGSÅ VED MELDESKJEMA TIL SLV

APPENDIX 3: DEFINITION OF EXPECTED DEATH AGE

folkehelseinstituttet

Kunnskap for folkets helse

søk

Forside > Helsestatistikk > Helsetilstanden i Norge

Stikkordsliste
A B C D E F G H I J
K L M N O P Q R S T
U V W X Y Z Æ Ø Å

Tema
Folkehelsestudier
Helsestatistikk
Statistikkalender
Statistikkoversikt
Helsetilstanden i Norge
Norgeshelsa (utvalgt statistikk)
Legemiddelstatistikk, grossistbasert
Kommunehelsa
Registre
Forskning og data
E-bøker

Kva er forventa og faktisk levealder

Publisert 07.02.2011 , Oppdatert: 08.02.2011, 16:30

Med uttrykket "forventa levealder ved fødselen" spår vi om framtida for dei som blir fødde i dag. Først om mange tiår kan vi få vite faktisk levealder for eit årskull barn.

Forventa levealder er det talet på år ein person kan vente å leve under gjeldande dødelegheitsforhold, og er ein prognose for levealderen i befolkninga. Oftast bruker vi t.d. berre uttrykket levealderen i 2005.

Dersom vi for eksempel ønskjer å vite forventa levealder for norske kvinner og menn i 2005, tar vi utgangspunkt i alderen på dei som døde året før (i 2004) og dei som overlevde 2005. Då kan det reknast ut kor gammal ein gutt og ei jente som blei fødde i 2005, vil bli i gjennomsnitt. Dette kallast forventa gjenståande levetid ved fødselen eller forventa levealder ved fødselen, og er ein prognose for levealderen i befolkninga. Oftast bruker vi berre uttrykket "levealderen i 2005". Statistisk sentralbyrå gjer kvart år slike utrekningar.

Forventa levealder kan også reknast ut for ulike aldersgrupper eller for eit fylke, ein bydel eller ein kommune. Men innbyggjartalet i det geografiske området må ha ein viss storleik for at utrekningane skal vere pålitelege.

Vi kan også rekne ut kor lenge vi har igjen å leve på ulike alderstrinn, for eksempel kor lenge ein 30- og 60-åring kan forvente å leve før dei døyr. Dette vert kalla forventa gjenståande levetid for 30-åringar, 60-åringar og så vidare.

Faktisk levealder for eit årskull kan vi først finne når alle i årskullet er døde. Ved dei noverande dødelegheitsforholda vil det ta meir enn 100 år; derfor må vi t.d. vente til minst 2111 for å få vite den faktiske levealderen for dei som vart fødde i 2011.

APPENDIX 4: PREVALENCE OF THE GENERAL POPULATION

Folkemengde 1. januar, etter region, kjønn, alder, tid og statistikkvariabel

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Totalt
	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer	Personer
0 Hele landet																				
Menn																				
0-9 år	288 861	294 529	299 717	304 291	308 347	311 842	312 714	313 942	312 893	310 374	308 096	306 773	305 334	303 697	302 731	303 016	305 524	308 298	310 404	5 811 383
10-19 år	281 341	276 649	272 561	270 386	270 526	272 357	275 919	281 270	286 645	292 562	298 554	303 769	309 264	314 521	319 363	323 746	325 651	327 703	328 780	5 631 567
20-29 år	344 812	344 818	341 557	336 350	329 350	322 582	316 305	309 967	305 233	298 216	293 331	288 619	285 060	284 378	287 454	295 232	304 001	311 342	321 102	5 919 709
30-39 år	324 241	325 966	329 143	332 071	335 025	338 353	342 744	347 464	350 392	352 832	355 430	355 589	353 801	351 247	348 256	348 269	348 036	345 837	345 826	6 530 522
40-49 år	309 897	314 896	316 426	317 607	315 471	314 635	315 029	317 143	318 438	320 646	322 749	324 867	328 863	333 284	338 802	346 104	353 875	360 114	365 989	6 234 835
50-59 år	196 153	203 588	214 515	226 393	240 872	253 537	264 773	274 544	282 894	291 402	298 193	302 936	304 669	306 425	305 685	306 854	308 955	311 944	315 169	5 209 501
60-69 år	183 796	178 962	174 794	171 328	168 987	168 189	168 293	169 340	170 838	172 165	176 130	183 099	193 680	205 314	219 273	231 236	241 907	251 303	259 638	3 688 272
70-79 år	141 536	142 765	143 786	143 814	143 912	142 601	141 365	140 413	138 259	136 420	134 850	132 772	130 911	129 325	128 840	129 271	130 400	132 571	135 112	2 598 923
80-89 år	50 275	50 883	52 084	52 874	53 900	55 215	56 399	56 912	59 340	60 733	61 989	63 590	65 158	66 240	67 502	67 774	68 178	68 743	69 141	1 146 930
90 år eller eldre	5 508	5 572	5 674	5 631	5 754	5 795	6 018	6 145	6 369	6 584	6 785	7 035	7 330	7 550	7 882	8 188	8 526	8 897	9 688	130 931
Kvinner																				
0-9 år	273 713	279 499	283 980	288 472	292 413	295 194	296 139	297 269	296 209	294 076	293 023	291 730	290 750	289 794	289 248	289 748	291 873	294 103	296 201	5 523 434
10-19 år	268 581	264 160	259 876	257 635	257 321	259 339	262 856	267 626	272 644	277 491	282 735	288 084	293 013	297 974	302 859	306 436	308 382	309 653	309 948	5 346 613
20-29 år	327 972	328 402	327 329	323 760	318 596	312 674	307 314	301 592	296 025	290 245	286 348	282 270	279 099	278 441	279 881	285 700	293 319	301 275	311 024	5 731 266
30-39 år	308 884	311 311	314 104	316 736	318 992	322 416	326 437	331 585	334 727	338 189	341 925	342 824	342 723	341 287	338 556	335 667	333 648	331 624	330 688	6 262 323
40-49 år	292 943	298 572	301 084	302 648	301 594	301 421	302 760	304 977	306 698	309 574	311 807	314 186	317 464	320 894	324 066	328 676	334 386	340 581	345 985	5 960 316
50-59 år	196 445	203 228	212 745	223 307	236 636	247 976	257 411	265 896	273 531	281 006	287 288	292 487	294 987	296 886	296 576	297 061	299 129	301 870	304 538	5 069 003
60-69 år	200 950	194 977	190 092	186 432	183 137	181 686	181 069	181 678	182 277	182 610	185 777	191 876	200 936	210 909	223 620	234 618	243 723	251 940	259 537	3 867 844
70-79 år	191 726	192 788	193 221	192 224	191 213	188 384	185 780	183 769	178 832	174 799	170 953	166 390	162 654	159 967	157 762	156 943	156 812	158 019	159 211	3 321 447
80-89 år	96 066	97 446	99 354	101 159	103 330	105 559	107 574	107 989	111 566	113 896	115 435	117 050	118 274	118 844	118 797	117 548	116 794	115 624	113 761	2 096 066
90 år eller eldre	15 467	15 804	16 368	16 839	17 338	17 844	18 430	18 976	19 626	20 246	20 854	21 511	22 393	23 242	23 981	25 084	26 133	26 758	28 563	395 457
Totalt																				
0-9 år	562 574	574 028	583 697	592 763	600 760	607 036	608 853	611 211	609 102	604 450	601 119	598 503	596 084	593 491	591 979	592 764	597 397	602 401	606 605	11 334 817
10-19 år	549 922	540 809	532 437	528 021	527 847	531 696	538 775	548 896	559 289	570 053	581 289	591 853	602 277	612 495	622 222	630 182	634 033	637 356	638 728	10 978 180
20-29 år	672 784	673 220	668 886	660 110	647 946	635 256	623 619	611 559	601 258	588 461	579 679	570 889	564 159	562 819	567 335	580 932	597 320	612 617	632 126	11 650 975
30-39 år	633 125	637 277	643 247	648 807	654 017	660 769	669 181	679 049	685 119	691 021	697 355	698 413	696 524	692 534	686 812	683 936	681 684	677 461	676 514	12 792 845
40-49 år	602 840	613 468	617 510	620 255	617 065	616 056	617 789	622 120	625 136	630 220	634 556	639 053	646 327	654 178	662 868	674 780	688 261	700 695	711 974	12 195 151
50-59 år	392 598	406 816	427 260	449 700	477 508	501 513	522 184	540 440	556 425	572 408	585 481	595 423	599 656	603 311	602 261	603 915	608 084	613 814	619 707	10 278 504
60-69 år	384 746	373 939	364 886	357 760	352 124	349 875	349 362	351 018	353 115	354 775	361 907	374 975	394 616	416 223	442 893	465 854	485 630	503 243	519 175	7 556 116
70-79 år	333 262	335 553	337 007	336 038	335 125	330 985	327 145	324 182	317 091	311 219	305 803	299 162	293 565	289 292	286 602	286 214	287 212	290 590	294 323	5 920 370
80-89 år	146 341	148 329	151 438	154 033	157 230	160 774	163 973	164 901	170 906	174 629	177 424	180 640	183 432	185 084	186 299	185 322	184 972	184 367	182 902	3 242 996
90 år eller eldre	20 975	21 376	22 042	22 470	23 092	23 639	24 448	25 121	25 995	26 830	27 639	28 546	29 723	30 792	31 863	33 272	34 659	35 655	38 251	526 388

APPENDIX 5: PREVALENCE OF CVD DEATH IN THE GENERAL POPULATION

Dødsfall av hjerte- karsykdommer, etter kjønn, alder, dødsårsak, tid og statistikkvariabel

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Totalt
	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall
Begge kjønn																				
0-9 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	2	6	8	10	4	8	6	9	2	3	6	7	8	4	7	3	4	5	5	107
10-19 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	5	4	12	10	4	5	5	4	7	6	3	7	7	5	8	3	4	5	6	110
20-29 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	22	23	25	16	22	14	23	18	12	9	11	12	11	12	13	13	16	11	8	291
30-39 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	55	70	70	61	69	46	64	66	62	69	60	48	63	61	58	50	42	41	43	1 098
40-49 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	297	288	272	272	249	248	265	208	207	183	191	193	155	194	191	167	149	166	196	4 091
50-59 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	723	644	623	662	605	560	631	634	599	648	602	531	589	522	517	492	508	434	425	10 949
60-69 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	2 497	2 333	2 117	2 112	1 753	1 620	1 569	1 531	1 331	1 254	1 231	1 127	1 061	1 035	1 033	1 088	1 087	1 070	1 037	27 886
70-79 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	6 514	6 534	5 931	5 921	5 671	5 579	5 441	5 068	4 577	4 315	4 106	3 588	3 209	2 855	2 693	2 586	2 368	2 269	2 207	81 432
80-89 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	8 054	8 251	7 770	8 054	8 139	8 356	8 340	8 438	8 266	8 124	8 029	7 743	7 434	6 727	6 674	6 776	6 455	6 126	5 702	143 458
90 år eller eldre																				
Sykdommer i sirkulasjonsorganene (I00-I99)	2 530	2 711	2 693	2 749	2 982	3 085	2 961	3 264	3 128	3 257	3 403	3 367	3 325	3 122	3 460	3 432	3 502	3 362	3 499	59 832

APPENDIX 6: PREVALENCE OF CVD DEATH AMONG GENDERS IN THE GENERAL POPULATION

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Totalt
	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall	Dødsfall
Menn																				
0-9 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	1	2	3	4	1	1	1	6	1	0	5	5	7	4	4	1	1	4	3	54
10-19 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	3	3	3	6	3	4	3	2	2	4	2	4	1	4	3	3	1	2	3	56
20-29 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	17	13	16	11	18	8	13	12	8	5	5	6	9	5	11	6	10	9	3	185
30-39 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	43	45	60	46	53	33	48	49	39	47	47	41	46	46	46	31	33	28	36	817
40-49 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	242	231	210	215	204	208	205	161	155	137	150	143	117	147	138	127	111	127	153	3 181
50-59 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	559	503	479	529	480	447	488	490	437	496	456	407	445	400	384	380	398	330	328	8 436
60-69 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	1 770	1 681	1 531	1 533	1 281	1 183	1 151	1 080	962	922	891	800	760	750	755	804	785	783	741	20 163
70-79 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	3 849	3 873	3 517	3 504	3 391	3 362	3 259	3 055	2 704	2 585	2 469	2 110	1 890	1 716	1 561	1 543	1 470	1 400	1 353	48 611
80-89 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	3 313	3 398	3 203	3 446	3 401	3 466	3 513	3 557	3 497	3 451	3 366	3 265	3 159	2 976	2 798	2 884	2 823	2 576	2 522	60 614
90 år eller eldre																				
Sykdommer i sirkulasjonsorganene (I00-I99)	765	739	745	722	819	812	766	815	854	892	930	887	859	838	895	963	969	944	963	16 177
Kvinner																				
0-9 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	1	4	5	6	3	7	5	3	1	3	1	2	1	0	3	2	3	1	2	53
10-19 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	2	1	9	4	1	1	2	2	5	2	1	3	6	1	5	0	3	3	3	54
20-29 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	5	10	9	5	4	6	10	6	4	4	6	6	2	7	2	7	6	2	5	106
30-39 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	12	25	10	15	16	13	16	17	23	22	13	7	17	15	12	19	9	13	7	281
40-49 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	55	57	62	57	45	40	60	47	52	46	41	50	38	47	53	40	38	39	43	910
50-59 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	164	141	144	133	125	113	143	144	162	152	146	124	144	122	133	112	110	104	97	2 513
60-69 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	727	652	586	579	472	437	418	451	369	332	340	327	301	285	278	284	302	287	296	7 723
70-79 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	2 665	2 661	2 414	2 417	2 280	2 217	2 182	2 013	1 873	1 730	1 637	1 478	1 319	1 139	1 132	1 043	898	869	854	32 821
80-89 år																				
Sykdommer i sirkulasjonsorganene (I00-I99)	4 741	4 853	4 567	4 608	4 738	4 890	4 827	4 881	4 769	4 673	4 663	4 478	4 275	3 751	3 876	3 892	3 632	3 550	3 180	82 844
90 år eller eldre																				
Sykdommer i sirkulasjonsorganene (I00-I99)	1 765	1 972	1 948	2 027	2 163	2 273	2 195	2 449	2 274	2 365	2 473	2 480	2 466	2 284	2 565	2 469	2 533	2 418	2 536	43 655