



Lipids, lipoproteins and prevalence of familial hypercholesterolemia in the Faroe Islands – Results from a nationwide laboratory database



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ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is one of the most common hereditary disorders. The population of the Faroe Islands was established by few founders, and genetic drift may have influenced lipid levels. The aim of this study was to describe the lipid distribution by providing age and sex-specific lipid values and to investigate the prevalence of FH in the Faroe Islands.

Methods: We used an electronic nationwide laboratory database that included lipid measurements obtained in the Faroe Islands between January 2006 and September 2020. Percentiles of lipid levels were calculated using quantile regression. The prevalence of FH was estimated according to the Make Early Diagnosis Prevent Early Death (MEDPED) diagnostic criteria and according to the LDL-C cut-off levels included in the Dutch Lipid Clinic Network (DLCN) criteria using generalized linear models with robust variance.

Results: According to the MEDPED age-specific cut-offs for LDL-C, a total of 216 subjects met the criteria for definite FH among 30,711 individuals corresponding to a prevalence of 0.70% (1:142). According to the LDL-C cut-offs included in the DLCN criteria, a total of 3,823 (1:8) subjects could be classified as having possible FH, and 10 (1:3,071) subjects could be classified as probable FH corresponding to a prevalence of 12.4% and 0.03%, respectively. Also, we found significant differences in lipid levels according to sex and age groups.

Conclusion: The Faroe Islands might represent a founder population with a prevalence of possible FH as high as 1 in 8. Further investigation of genetic and clinical characteristics of FH in the Faroe Islands is needed.

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Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by severely elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. Several diagnostic criteria have been developed to diagnose FH based on plasma LDL-C levels, clinical and family history of cardiovascular disease (CVD), clinical findings and genetic mutations [1–3].

LDL-C is a causal factor for the development of atherosclerosis

[4,5] and untreated patients with FH have a considerably increased risk of premature atherosclerotic cardiovascular disease (ASCVD) and premature death [5,6]. For a long time the prevalence of FH was believed to be approximately 1 in 500, but recent meta-analyses have suggested a prevalence of around 1 in 300 which makes FH the most common monogenic disorder [7,8]. The prevalence may vary according to definition used and the population studied as much higher prevalence of FH has been reported in certain founder populations [9].

The Faroe Islands are an isolated archipelago in the North Atlantic Ocean, founded by a small number of settlers around 850 AD. The population size was around 4000 inhabitants in the late 1300s and remained limited for many centuries due to the isolated

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geographic location, but during recent years the population growth has increased rapidly to approximately 52,000 inhabitants [10,11]. The population of the Faroe Islands is considered the genetically most homogenous population in the North Atlantic Region [10,11]. Consequently, several genetic disorders are very prevalent in the Faroe Islands [12–15], but the prevalence of FH is unknown.

The objective of this study was to describe the lipid distribution of the major lipids and lipoproteins including total cholesterol (total-C), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides in the Faroe Islands by providing age- and sex-specific lipid values. Furthermore, we aimed to estimate the prevalence of FH according to the Make Early Diagnosis Prevent Early Death (MEDPED) diagnostic criteria and according to the LDL-C cut-off levels included in the Dutch Lipid Clinical Network (DLCN) diagnostic criteria.

Materials and methods

All blood samples in the Faroe Islands are analyzed at hospital laboratories and registered in an electronic nationwide laboratory database (BCC-Web, CGI). We studied lipid and lipoprotein measurements obtained in the Faroe Islands between January 2006 and September 2020 from this database. The database also includes information on birthdate and civil registration number, sample date, and whether the samples were fasting or non-fasting. Plasma LDL-C values in the database were calculated in mmol/L according to the Friedewald formula [16,17].

We excluded individuals with a foreign civil registration number and individuals without a complete lipid profile (total-C, LDL-C, HDL-C and triglycerides). According to local practice, LDL-C values that were calculated, despite triglyceride levels exceeding 4 mmol/L, were excluded as the Friedewald equation is not valid for such values [16,18].

We categorized subjects registered with a complete lipid profile according to the MEDPED diagnostic criteria and the LDL-C cut-offs included in the DLCN diagnostic criteria for heterozygote FH, respectively (Table 1). Both criteria were based on the highest registered plasma LDL-C level in each individual. The MEDPED criteria is based on age-specific cholesterol cut-offs (total-C or LDL-C), and we defined individuals as having FH if the highest measured cholesterol level exceeded one of these cut-offs (Table 1). According to the LDL-C cut-offs included in the DLCN criteria, probable FH was defined as LDL-C ≥ 8.5 and possible FH as LDL-C ≥ 5 mmol/L.

Statistical analyses

We used quantile regression to estimate the 1th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 99th percentiles for plasma total-C, LDL-C, HDL-C and triglycerides based on first registered lipid levels. We

estimated the prevalence proportion of FH with corresponding 95% confidence intervals using generalized linear models with robust variance estimation. The statistical analyses were conducted using Stata (version 16, StataCorp, US).

Results

We identified a total of 191,336 complete individual measurements of plasma total-C, HDL-C and triglycerides among 30,831 individuals comprising 15,827 men and 15,004 women, while 186,305 values of calculated LDL-C were available among 30,711 individuals comprising 15,730 men and 14,981 women. In women, the distribution across age-intervals was as follows: 428 (2.9%) <18 years, 3,760 (25.1%) 18–39 years, 7,430 (49.6%) 40–64 years and 3,363 (22.5%) aged above 65 years. The distribution in men across age-intervals was 373 (2.4%) <18 years, 3,881 (24.7%) 18–39 years, 8,336 (53.0%) 40–64 years and 3,140 (20.0%) aged above 65 years, respectively.

Plasma lipids and lipoproteins in men and women

The overall median plasma total-C was 5.2 mmol/L (1th percentile 2.7, 99th percentile 7.7) for men and 5.3 mmol/L (1th percentile 3.0, 99th percentile 8.2) for women (data not shown).

The overall median plasma LDL-C was 3.3 mmol/L (1th percentile 1.1, 99th percentile 5.5) for men and 3.2 mmol/L (1th percentile 1.0, 99th percentile 5.7) for women. In men, LDL-C levels increased by age groups from birth to reach a maximum among subjects aged 45–50 years (median 3.6, 95th percentile 5.3). Subsequently, we observed a gradual decrease in LDL-C levels in older age groups where men aged 75–80 years (median 2.9, 95th percentile 4.8) had markedly lower LDL-C levels than those aged 45–50 years (median 3.6, 95th percentile 5.3).

In women, LDL-C levels also increased by age groups, but the slope was lower than in men, although median levels increased markedly from 35 years of age and peaked in subjects aged 60–65 years (median 3.7, 95th percentile 5.4). In women above 65 years of age, we also observed a gradual decrease in LDL-C levels, but the slope of the curve was more flattened compared to men (Fig. 1). In post hoc analyses, we performed a linear regression among men aged above 50 years, showing a 0.22 mmol/L decrease in LDL-cholesterol for every ten-year increase in age (p-value <0.001). In women above 60 years, we observed a 0.18 mmol/L decrease in LDL-cholesterol for every ten-year increase in age (p-value <0.001). These associations were statistically significant as indicated, but modest.

The overall median plasma HDL-C was 1.2 mmol/L (1th percentile 0.6, 99th percentile 2.4) for men and 1.5 mmol/L (1th percentile 0.7, 99th percentile 2.7) for women. In men, median HDL-C levels

Table 1

Estimated prevalence proportion of FH in the Faroese population according to the MEDPED and DLCN diagnostic criteria based on cholesterol levels.

| | Individuals meeting the criteria (n) | Total number of individuals (n) | Prevalence (95% CI) | |
|--------------------------|--------------------------------------|---------------------------------|------------------------|--------|
| MEDPED | | | | |
| Total-C ^a | 252 | 30,831 | 0.82% (0.72; 0.92%) | 1:122 |
| LDL-C ^b | 216 | 30,711 | 0.70% (0.62; 0.80%) | 1:142 |
| DLCN | | | | |
| Possible FH ^c | 3,823 | 30,711 | 12.45% (12.08; 12.82%) | 1:8 |
| Probable FH ^d | 10 | 30,711 | 0.03% (0.02; 0.06%) | 1:3071 |

Abbreviations: DLCN, Dutch Lipid Clinic Network; MEDPED, Make Early Diagnosis Prevent Early Death.

^a Total-C (mmol/l) > 7.0 (<20 years), > 7.5 (20–29 years), > 8.8 (30–39 years) or > 9.3 (≥ 40 years).

^b LDL-C (mmol/l) > 5.2 (<20 years), > 5.7 (20–29 years), > 6.2 (30–39 years) or > 6.7 (≥ 40 years).

^c LDL-C (mmol/l) ≥ 5.0 mmol/l.

^d LDL-C (mmol/l) ≥ 8.5 mmol/l.

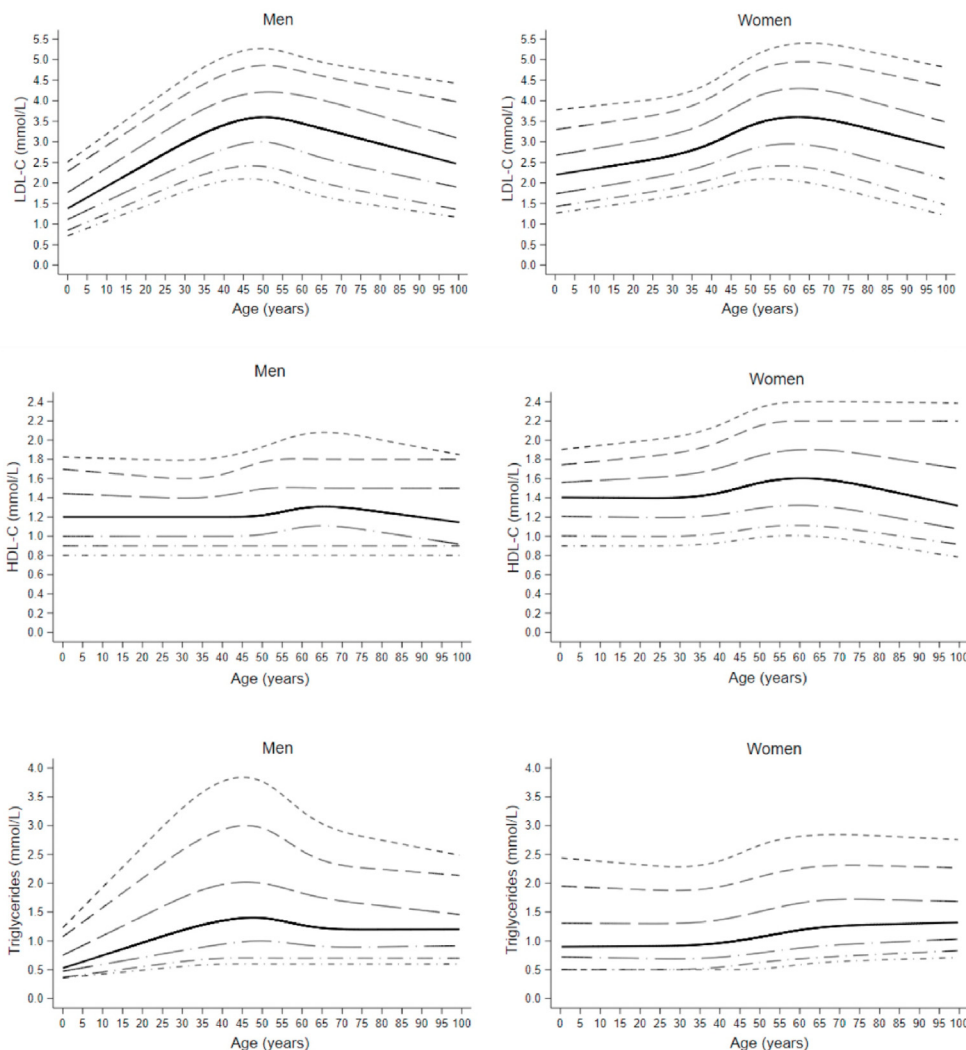


Fig. 1. Age and sex related levels of LDL-C, HDL-C and triglycerides in men (left) and women (right). The 5th, 10th, 25th, 50th, 75th, 90th and 95th percentile curves.

were similar throughout all age groups ranging from 1.1 to 1.5 mmol/L. In women, median HDL-C levels ranged from 1.1 to 1.6 mmol/L with slightly higher median HDL-C levels above 50 years of age and slightly lower values in older age groups (>75 years) (Fig. 1).

The overall median plasma triglyceride levels were 1.3 mmol/L (1st percentile 0.5, 99th percentile 5.1) for men and 1.1 mmol/L (1st percentile 0.4, 99th percentile 4.0) for women. In men, we observed gradually higher triglyceride levels from childhood (median 0.7, 95th percentile 2.5) to reach a maximum at 45–50 years of age (median 1.4, 95th percentile 3.9). In age groups above 55 years, we observed slightly lower triglyceride levels in men. Triglyceride levels in women were relatively similar throughout all age groups ranging from 0.9 to 1.3 mmol/L (Fig. 1).

Prevalence of FH

According to the MEDPED age-specific cut-offs for total-C, a total of 252 subjects met the criteria for definite FH among 30,831 individuals corresponding to a prevalence of 0.82% (95%CI: 0.72; 0.92%) or 1 in 122. Among 30,711 individuals, a total of 216 subjects fulfilled the LDL-C cut-offs for definite FH according to MEDPED,

corresponding to a prevalence of 0.70% (95%CI: 0.62; 0.80%) or 1 in 142 (Table 1).

The prevalence of definite FH across age intervals included in the MEDPED criteria for total-C was 0.87% (95% CI 0.47;0.92) in those aged below 20 years, 1.55% (95% CI 1.13;2.13) in those aged 20–29 years, 0.37% (95% CI 0.22;0.63) in those aged 30–39 years and 0.81% (95% CI 0.70;0.93) among those aged 40 years and above. According to the MEDPED criteria based on LDL-C, the prevalence across age intervals was 0.35% (95% CI 0.13;0.92), 0.41% (95% CI 0.22;0.78), 0.40% (95% CI 0.24;0.66) and 0.80% (95% CI 0.69;0.92), respectively.

According to the LDL-C cut-offs included in the DLCN criteria, a total of 3,823 (1 in 8) subjects were classified as having possible FH, and 10 (1 in 3,071) subjects as having probable FH corresponding to a prevalence of 12.4% (95%CI: 12.1; 12.8%) of possible and 0.03% (95%CI: 0.02; 0.06%) of probable FH, respectively (Table 1).

We found a significant difference in FH prevalence among men and women. Thus, 1 in 113 women (0.89%) had definite FH according to the MEDPED criteria, while the prevalence for men was 1 in 187 (0.53%). According to the LDL-C cut-offs included in the DLCN score for possible FH, 11.53% of men and 13.42% of women had an LDL-C ≥5 mmol/L, respectively.

Discussion

In this paper we present the distribution of plasma lipid and lipoprotein levels in the Faroese population based on a large nationwide clinical laboratory database covering all blood samples collected over a 14-year period. We found major differences in lipid levels according to sex and age groups, which may be useful in clinical practice. Interestingly, we found a very high prevalence of definite FH in the Faroe Islands according to the MEDPED criteria (1 in 122 based on total-C and 1 in 142 based on LDL-C) and an extremely high prevalence of possible FH (1 in 8) according to the LDL-C cut-off levels included in the DLCN criteria (LDL-C ≥ 5.0 mmol/L). Furthermore, we observed a higher prevalence of clinical FH in women compared to men. Unfortunately, our data did not allow for calculation of prevalence estimates separately among men and women within age intervals included in the MEDPED criteria as few cases of FH were identified among those aged below 40 years of age as expected as most individuals tend to have lipid measurements performed in mid-life in clinical practice.

The strengths of this study were the use of a nationwide clinical laboratory database including all lipid measurements undertaken in the Faroe Islands from 2006 to 2020. Samples were available for almost 60% of the entire Faroese population, with lipid levels representing individuals from 0 to 100 years of age. However, this study also had some limitations. Thus, the estimated prevalence of FH according to the DLCN criteria was based on LDL-C levels alone, as we did not have access to clinical and family history, clinical manifestations of FH (xanthomas, arcus cornealis) or genetics. Therefore, we may have underestimated the prevalence of FH. Neither did we have information on lipid-lowering treatment or possible secondary causes of dyslipidemia which might lead to underestimation and overestimation of the true prevalence of FH, respectively.

Limited data exist regarding detailed age- and sex-specific percentile-based reference values in the general population of lipids and lipoproteins. However, we observed similar age- and sex-specific lipid distributions as reported in a cohort study including a total of 133,500 individuals from the Netherlands [19]. Also, we observed similar patterns of LDL-C levels according to sex and age as a recent large Danish cohort study including 559,889 individuals [20].

Limited data exist on estimated FH prevalence based on laboratory databases. Casula et al. [21] used electronic data in 162,864 individuals from Italy to estimate the FH prevalence. In addition to lipids and lipoproteins, they also had information on history of CVD and prescription of lipid-lowering medications. According to a partial assessment of the DLCN score, they reported a prevalence of possible FH of 3.4% in statin-treated and 2.9% in untreated subjects. The prevalence of probable FH was 0.02% among statin-treated and 0.01% among untreated subjects. The prevalence of definite FH according to the MEDPED criteria was 0.18% (1:540) in statin-treated and 0.07% (1:1,380) in untreated subjects, respectively. Thus, the prevalence of FH according to these diagnostic criteria was markedly higher in our study than in the study by Casula et al. [21].

A recent large meta-analysis of 11 million individuals including 33,036 patients with FH found a prevalence of FH in 1 in 313 [7]. However, an even higher prevalence - up to 1 in 100 - may exist in certain founder populations [9]. The Faroe Islands were settled by a small number of individuals and the very high prevalence of definite and possible FH found here could indicate that this population represents a new FH founder population.

Plasma cholesterol levels are controlled by both genetic and environmental factors. Genetic FH is typically caused by mutations encoding the LDL-receptor, the ligand apolipoprotein B, or the

proprotein convertase subtilisin/kexin type 9, which is involved in the degradation and recirculation of the LDL-receptor [6]. Most founder populations are characterized by a few pathogenic mutations dominating within the population [22–26]. The importance of environmental factors on LDL-C levels in the Faroe Islands remains uncertain. However, traditional Faroese cuisine is dominated by animal products and is high in saturated fat. Important parts of traditional Faroese food are fish, lamb, seabirds, whale meat and blubber, but today's food is much more similar to most western populations. Further assessment of possible explanations for the highly elevated cholesterol levels in the Faroe Islands, both related to inheritance and lifestyle, is warranted.

In conclusion, the Faroe Islands might represent a founder population with a prevalence of possible FH as high as 1 in 8. Further investigation into the genetic and clinical characteristics of FH in the Faroe Islands should be undertaken.

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Author contributions

All authors contributed to the conceptualization of the project. Sáb wrote the first draft of the manuscript and conducted the statistical analyses and prepared tables and figures. CSB, MSN, SLC, EBS and AMJ contributed to the planning of the statistical analyses and interpretation of the data. CSB and SLC supervised the conduct of the statistical analyses. All authors have contributed to the content and have approved the final version of the manuscript.

Declaration of competing interest

The authors did not declare any conflict of interest.

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