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Genetic testing is essential for initiating statin therapy in children with familial hypercholesterolemia: Examples from Scandinavia

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A B S T R A C T

Background and aims: In familial hypercholesterolemia (FH), statin treatment should be considered from 8 to 10 years of age, but the prevalence of statin use among children is not known.

Methods: Statin use (2008–2018) among children aged 10–14 and 15–19 years was obtained from the national prescription databases in Norway, Sweden and Denmark. We assumed that all statin users in these age groups had FH, and that the estimated prevalence of FH is 1 in 250 inhabitants. Changes in prevalence rates of statin use between 2008 and 2018 by country, age and sex were estimated using the Joinpoint Regression Program version 4.8.0.1. Differences in prevalence rate ratio each year between countries were analyzed using Poisson regression.

Results: Among children aged 10–14 years, there was a significant increase in statin use in Norway and Denmark between 2008 and 2018, while in Sweden an increase was only seen after 2014. Among children aged 15–19 years, an increase in statin use was only observed in Norway and Sweden between 2008 and 2018. Statin use was significantly more prevalent in Norway than in Sweden and Denmark each year, and in 2018 the proportion of children using statins was 4–5 times (10–14 years) and 3 times (15–19 years) higher in Norway compared with Sweden and Denmark. In 2018 in Norway, 19% and 35% of children aged 10–14 years and 15–19 years estimated to have FH used statins respectively; corresponding percentages in Sweden were 4.5% and 10%, and in Denmark 3% and 12%. In Norway, the increase in statin use between 2008 and 2018 roughly corresponded to the increase in children with genetically verified FH.

Conclusions: Between 2008 and 2018, statin use increased in children aged 10–19 years in Norway, Sweden and Denmark, but with large differences between the countries; statin use was 3–5 times more prevalent in Norway than in Sweden and Denmark, which may be due to a more widespread use of genetic testing for FH in Norway.

1. Introduction

Due to the lifetime exposure to high low density lipoprotein (LDL) levels in familial hypercholesterolemia (FH), statins as first drug of choice should be considered to be initiated at 8–10 years of age [1,2]. Little data exist, however, on the extent to which children with FH are treated according to these recommendations. Within the Scandinavian countries, Norway, Sweden and Denmark, there are different approaches to genetic testing for FH. In Norway, genetic testing for FH is centralized to one laboratory, the Unit for Cardiac and Cardiovascular Genetics (UCCG) at Oslo University Hospital, whereas in Sweden and Denmark, genetic testing is performed by multiple laboratories. This could result in diagnostic and treatment differences in individuals with FH.

The worldwide prevalence of FH has been estimated to be 1 in 313 individuals in the general population [3]. In Denmark, the prevalence of

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FH has been found to be 1 in 217 in a large general population study [4]. In the other two Scandinavian countries, Norway and Sweden, general population screening for FH has not been done. In this study, we assumed a similar and approximate prevalence of FH of 1 in 250 individuals in Norway, Sweden, and Denmark. Since statins in childhood are seldom used in other conditions than in FH, we also assumed that all statin users in the age range 10–19 years have FH.

The aim of this study was to report prevalence rates of statin use in children aged 10–14 years and 15–19 years, and the proportion of statin users among those estimated to have FH in Norway, Sweden and Denmark in the period from 2008 through 2018. In Norway, we also describe the correspondence between individuals with genetically verified FH and statin users in the ages 10–19 years.

2. Materials and methods

In the Scandinavian countries, statins are only available through prescriptions, and data on dispensed drugs can be accessed through each country's national prescription database [5–7]. We obtained aggregate data on unique (identified by person identification number as used in the Scandinavian countries) statin users [at least one dispensed prescription per year of either ATC code C10AA (statins) or C10BA (statins in combination with ezetimibe)] from the prescription databases in the two predefined age groups 10–14 years and 15–19 years between 2008 and 2018. Population data by 1 January each year according to age groups (10–14 and 15–19 years) and sex were obtained from national statistics.

Proportion of individuals with FH (as estimated by a population prevalence of 1:250) using statins was calculated as follows: statin prevalence rate per 1000 inhabitants/4, and was presented as percentage (%) with standard deviation (SD). Additionally, from the UCCG database in Norway, we obtained the number of individuals with genetically diagnosed FH in the age groups 10–14 years and 15–19 years between 2008 and 2018.

To identify changes in statin use over time, prevalence rates by country, age group and sex were estimated using the Joinpoint Regression Program version 4.8.0.1 (Statistical Research and Applications Branch, National Cancer Institute). This method identifies the year (s) where a change in the rate of statin users (per 100,000) is present, and calculates the annual percentage change (APC) between trend-change points during the period 2008–2018. As the age-band was narrow (10–19 years), and as only aggregate data for two age groups were available, rates were presented by age group and not age-standardized. Poisson regression with prevalence rate ratios (PRR) was used to compare statin use between countries stratified by year, sex and age groups and adjusted for population base. Kendall's tau correlation was used to assess the correlation between number of statin users and number of children with genetically verified FH in corresponding age groups. Poisson regression analyses and correlation tests were performed using Stata version 16. The significance level was set at 0.05 and all tests were two-sided.

This study did not need consent or ethical approval due to the use of anonymous, aggregated data that are freely available online.

3. Results

The PRR analysis for difference in statin use between sexes was non-significant, and we therefore only present results for boys and girls combined in both the 10–14 years and 15–19 years age groups.

In the 10–14 years age group, there was a significant increase in statin use between 2008 and 2018 in Norway [APC 16.3% (95% CI: 14.5–18.1)] and Denmark [(APC 12.1 (95% CI: 8.0, 16.3)], and in Sweden between 2014 and 2018 [APC 31.8 (95% CI: 17.3, 48.0)] (Fig. 1). In 2018 in Norway, statin use was proportionally 4.2-times higher than in Sweden and almost 5 times (4.7) higher than in Denmark (Table 1).

In the 15–19 years age group, there was a significant increase in statin use between 2008 and 2018 in Norway and Sweden, with the steepest increase after 2013 in Norway [(APC 7.2 (95% CI: 4.8, 9.7)] and after 2016 in Sweden [APC 22.4 (95% CI: 3.4, 44.8)]. No significant increase in statin use was observed in Denmark during 2008–2018

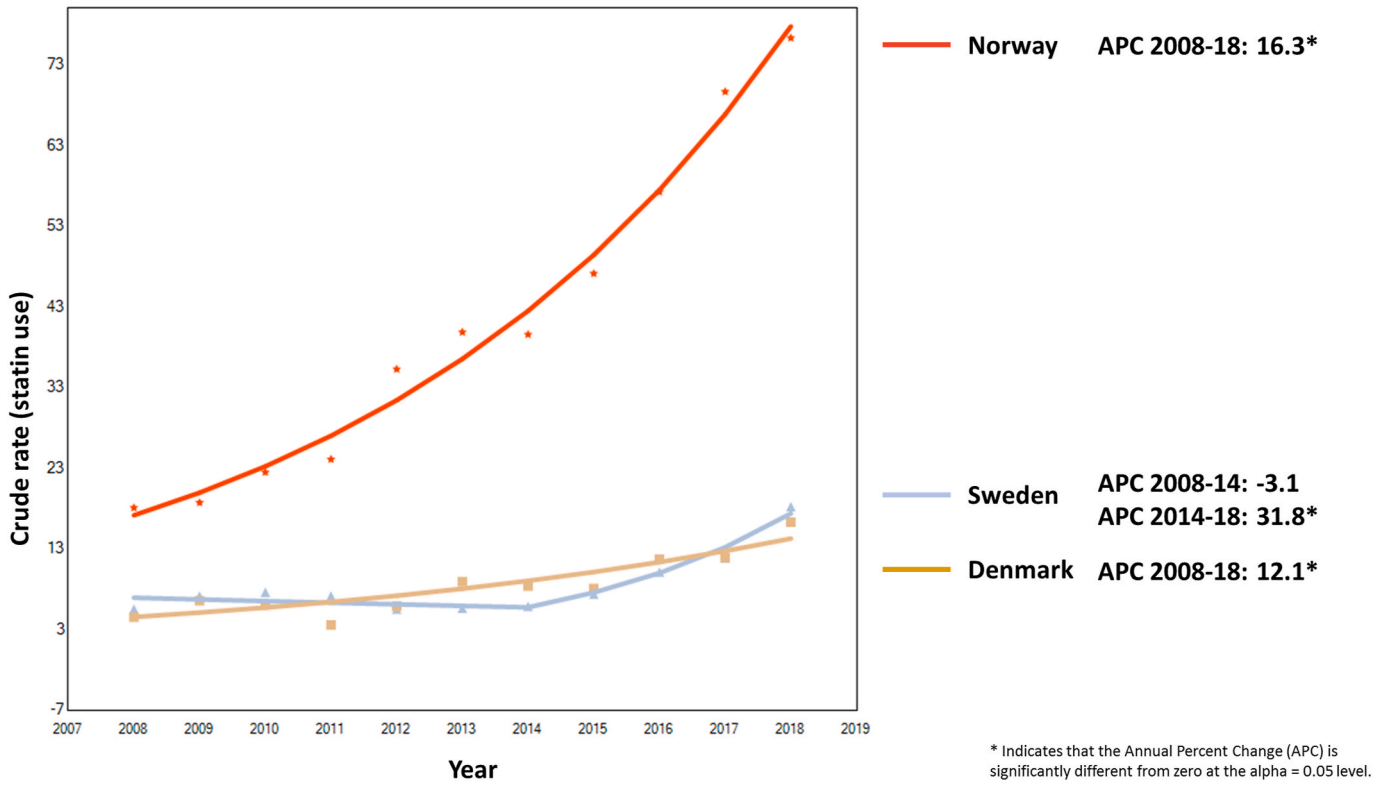

Fig. 1. Trends in statin use in children aged 10–14 years in Norway, Sweden and Denmark between 2008 and 2018 in boys and girls combined.

Table 1
Statin use among children aged 10–14 years and 15–19 years (both sexes combined) in Sweden and Denmark compared with Norway in 2018.

	10–14 years			15–19 years		
	Statin prevalence rate[a]	Proportion (%) of children with FH[b] using statins	PPR (95%CI)	Statin prevalence rate[a]	Proportion (%) of children with FH[b] using statins	PPR (95%CI)
Sweden (ref.)	0.18 ± 0.04	4.5 ± 1.0	1	0.39 ± 0.02	9.9 ± 0.4	1
Norway	0.76 ± 0.03	19.0 ± 0.7	4.2 (95% CI: 3.2–5.3)	1.42 ± 0.08	35.4 ± 1.9	3.6 (95% CI: 3.05–4.22)
Denmark (ref.)	0.10 ± 0.06	2.7 ± 1.6	1	0.48 ± 0.06	12.1 ± 1.5	1
Norway	0.76 ± 0.03	19.0 ± 0.7	4.7 (95% CI: 3.5–6.3)	1.42 ± 0.08	35.4 ± 1.9	2.9 (95%CI: 2.42–3.44)

[a] Per 1000 inhabitants.
[b] FH as estimated on population prevalence of 1:250. PPR, prevalence rate ratio; FH, familial hypercholesterolemia.

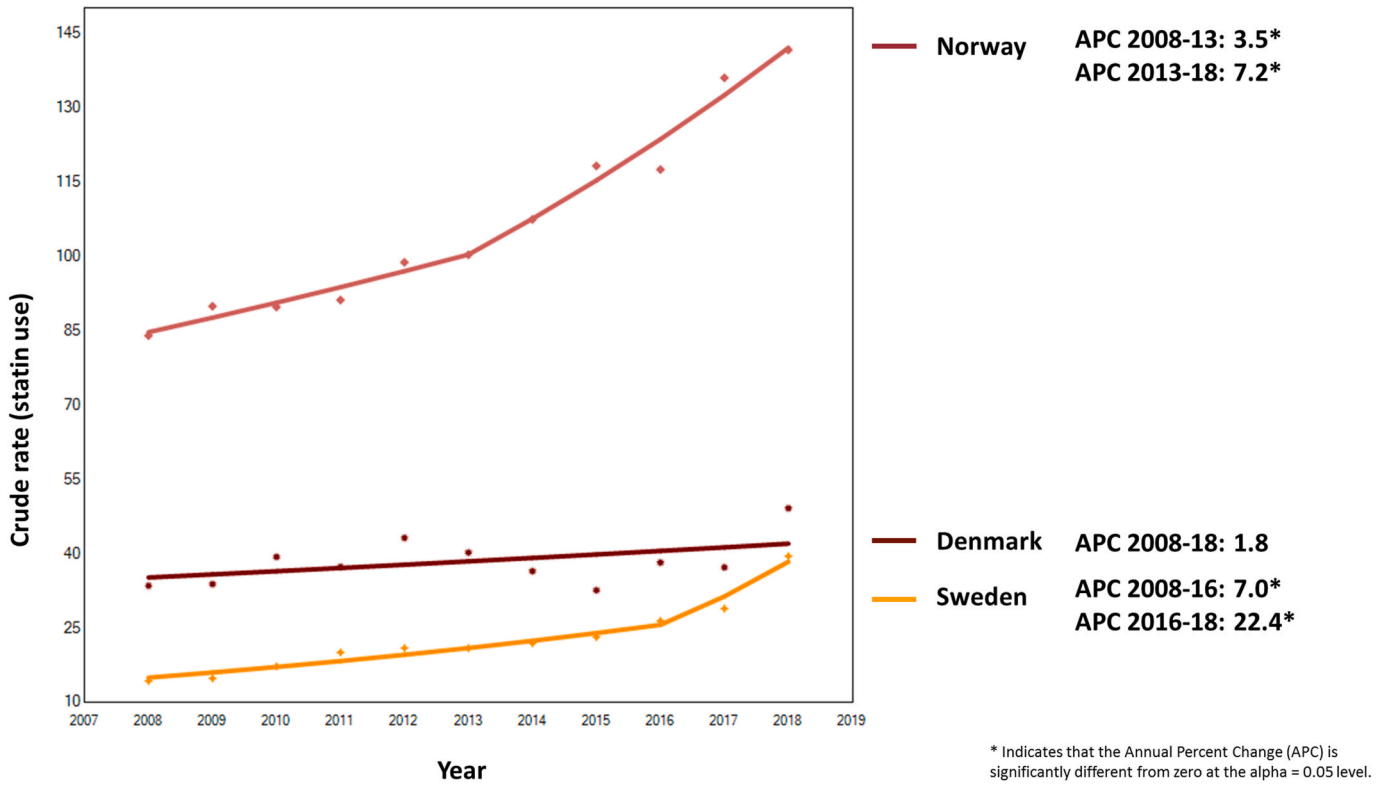

Fig. 2. Trends in statin use in children aged 15–19 years in Norway, Sweden and Denmark between 2008 and 2018 in boys and girls combined.

(Fig. 2). In Norway in 2018, statin use was proportionally 3.6 times higher than in Sweden, and 2.9 times higher than in Denmark (Table 1).

In Norway in 2018, the estimated proportion of children with FH using statins was 19.0 % (SD 0.7) in the age group 10–14 years, and 35.4 % (SD 1.9) in the age group 15–19 years; corresponding prevalence for Sweden was 4.5% (SD 1.0) and 9.9% (SD 0.4), and for Denmark, 2.7% (SD 1.6) and 12.1% (SD 1.5), respectively (Table 1).

Of the children with genetically verified FH aged 10–19 years in Norway, 83% (n = 836) were likely to use statins (Fig. 3). The Kendall's tau correlation between number of genetically verified FH children and number of statin users was 0.96, $p < 0.001$.

4. Discussion

This is the first study to investigate statin treatment rates over a 10-year period in children aged 10–19 years. Statin treatment from childhood is probably safe, reducing the lifelong elevated LDL burden and most likely the risk of premature coronary heart disease [8,9]. The overall increase in statin use in all three countries among children aged 10–14 years is therefore reassuring, whereas the lack of increase in statin use among children aged 15–19 years in Denmark should be further investigated. We did not observe differences in statin use between sexes in any of the countries, which is in line with data from the UK Paediatric FH register [10], whereas other countries have found slightly higher on-treatment rates in boys [11]. Although there may be reasons for not treating some children with FH [1,12], the treatment rates in our study are too low, particularly in Sweden and Denmark. Data from eight European countries show that many children with FH do not receive recei appropriate lipid-lowering treatment [11]. In 2018, statin use was 4–5 times higher in children aged 10–14 years and 3 times higher in children aged 15–19 years in Norway than in children from Sweden and Denmark. Even though the Scandinavian countries share many features regarding the health care system and social security, one reason for the marked differences in statin use between the three countries may be differences in policies and public health efforts on FH, including the use of genetic testing. In Norway, genetic testing for FH has been part of the national health care system, with a centralized reimbursement system of all testing since 1998, and all medical doctors can request a genetic test for FH at any age. In Sweden and Denmark, testing for FH is usually performed from age 8–16 years at request from a specialist, and costs for

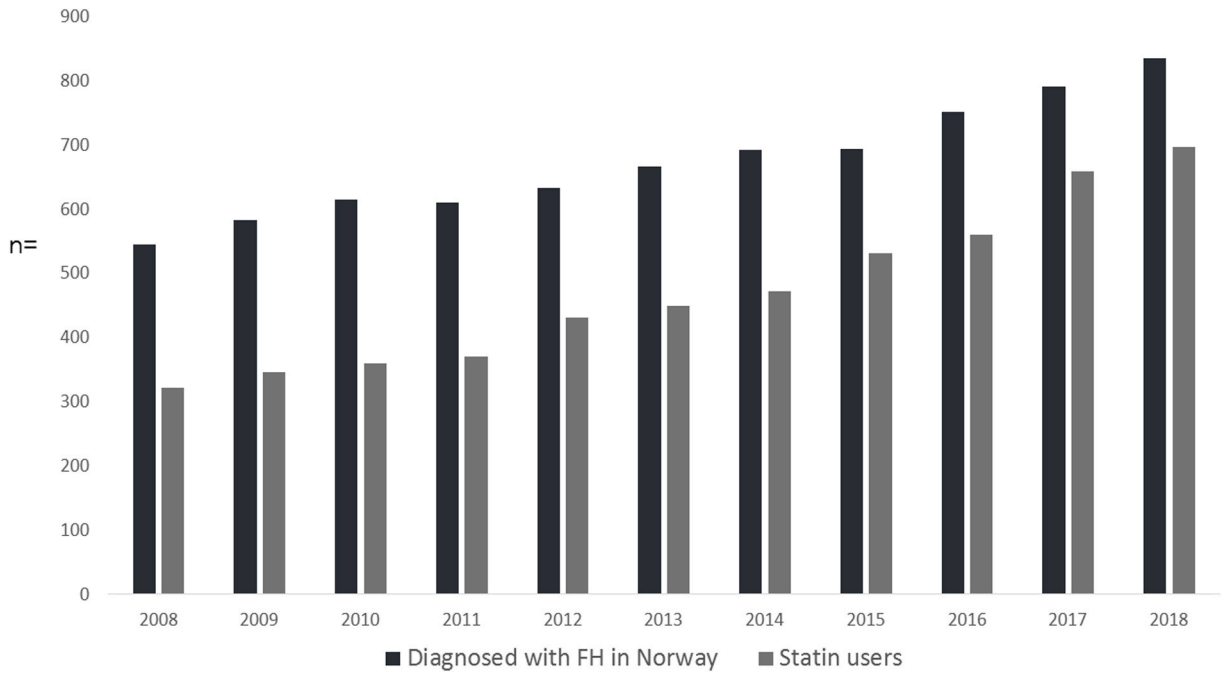

Fig. 3. Number of genetically diagnosed children aged 10-19 years with familial hypercholesterolemia and number of statin/statins + ezetimibe users in corresponding age group in Norway between 2008 and 2018.
The Kendall's tau correlation = 0.96, $p < 0.001$.

genetic testing must be covered by the local hospitals. This is likely to result in a higher threshold for genetic testing in Sweden and Denmark.

Based on aggregate data from Norway, we observed a strong correspondence between the number of statin users and the number of individuals with genetically verified FH between 2008 and 2018. This could indicate that to increase treatment rates, more children need to be genetically diagnosed with FH, as supported by Leren et al. [13] and an European study where countries with the highest percentage of children identified with an FH mutation also had the highest percentage on statin treatment (such as Greece and The Netherlands) [11]. However, we cannot claim any causal relation in this study, and studies of data at an individual level are warranted to adequately address the association between statin use and genetically verified FH.

The majority of children with FH are diagnosed through family cascade screening. To find children with FH, parents need to be diagnosed and a positive genetic test in a parent is a strong incentive to perform family genetic screening. Genetic cascade screening in FH is considered to be cost-effective [14], and centralized, reimbursed genetic testing as in Norway could be a useful approach to lower the threshold for testing. In the Netherlands, as well as in Norway, genetic testing for FH with subsequent family cascade screening for FH has been practiced systematically since the 1990s [15]. The Netherlands and Norway are also the two countries in the world with the highest detection rates of FH [16]. Hence, in our opinion, also shared by others, a genetically confirmed diagnosis of FH is essential both for treatment of the affected individual and for finding and treating other affected family members [13,16]. The differences in statin use between Norway and the other Scandinavian countries in our study supports this view.

4.1. Strengths and limitations

We obtained data on statin use from national population-based registries, which ensures we have an almost complete and unbiased follow-up. There are some limitations to the interpretation of our results. The number of individuals with FH is an estimate and the true prevalence of FH may be different in Norway, Sweden and Denmark. Furthermore, we present data on dispensed prescriptions, but we do not know if the dispensed drugs have been used. Some children may have been prescribed statins for other reasons than FH. However, we could assume that these limitations do not differ much between the three countries, and are not likely to have an impact on the observed differences in statin use between the countries. Since our aggregate data were based on the number of unique users in the two ATC groups C10AA and C10BA, there is a possibility that one individual could have been counted twice if they switched from one ATC group to another during the same year, leading to overestimation of the number of users. However, the relevance of this limitation is limited due to the small number of users in the ATC group C10BA (statins + ezetimibe) in all three countries, as supported by others [11].

In conclusion, between 2008 and 2018, statin use increased among children aged 10–14 years in Norway, Sweden and Denmark and among children aged 15–19 years in Norway and Sweden, with large differences between countries. In 2018, statin use was 4–5 times more prevalent in 10–14 year old children, and 3 times more prevalent in 15–19 year old children in Norway than in Sweden and Denmark. Differences in the use of genetic testing between countries may be the main reason for these differences in treatment rates. Increased awareness of the importance of early diagnosis of FH in children, and early initiation of treatment in children with known FH are needed among parents, general practitioners, pediatricians, cardiologists, and in lipid clinics.

Author contributions

KS, GL, HWK, KBH, MPB, JB, ICK & KR contributed to the conceptualization and methodology of the project. KS, GL, JSS, MPB, KR had the main responsiblity for the use of software, validation, formal analysis and visualization. KS, GL, JSS, MPB, KR, JB, ICK contributed to investigation, data curation and provison of resources. All authors critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: HWK and JSS declare no conflict of interest. KS has received consulting/advisory fees from MedXplore; not relevant for this manuscript. GL has received lecture and advisory board fees from Amgen, Sanofi and Boehringer, none of which are relevant for this manuscript. JB has received consulting/advisory board fees from Akcea Therapeutics, Amgen, MSD and Sanofi, and investigator-initiated study grants from Amgen and Sanofi; none of which are relevant for this manuscript. ICK has received lecture fees from Sanofi and MSD, none of which are relevant for this manuscript. KBH has received lecture and/or advisory board fees from Amgen and Sanofi, none of which are relevant for this manuscript. MPB reports personal fees from Sanofi, Amgen, Boeheringer Ingelheim, Mills DA and grants from Kaneka, none of which are relevant for this manuscript. KR reports personal fees from Amgen, Mills DA, MedExplore, The Norwegian Medical Association,The Norwegian Directorate of Health, Sanofi, Sunovion and Bayer, none of which are relevant for this manuscript.

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