

Long-Term Cardiovascular Risk in Heterozygous Familial Hypercholesterolemia Relatives Identified by Cascade Screening

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Background—Heterozygous familial hypercholesterolemia increases the risk of adverse cardiovascular events. Whether affected relatives of probands are at increased risk remains unknown. We aimed to evaluate the long-term cardiovascular risk in heterozygous familial hypercholesterolemia relatives with a low-density lipoprotein receptor (*LDLR*) mutation who were all recommended statin therapy.

Methods and Results—Participants were identified by cascade screening at Aarhus University Hospital during 1992–1994. A comparison cohort from the Danish general population was matched 10:1 to relatives by birth year and sex. Using medical registries, participants were followed until the event of interest, migration, death, or end of follow-up on December 31, 2014. The primary end point was all-cause mortality and major adverse cardiovascular events comprising myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, and coronary revascularization. We included 220 relatives. Median age was 37 years (interquartile range: 27–52 years) of which 118 (54%) had an *LDLR* mutation. By 2004, when prescription data became available, 89% of mutation-carrying participants were taking statins during their follow-up period. Despite frequent use of lipid-lowering medication, the adjusted hazard ratio of the primary end point was 1.65 (95% confidence interval, 1.17–2.33) in mutation-carrying relatives compared with the general population cohort. The risk in non-mutation-carrying relatives was not different from that of the general population cohort (adjusted hazard ratio: 0.85; 95% confidence interval, 0.56–1.29). Comparing mutation-carrying relatives with non-mutation-carrying relatives, the adjusted hazard ratio was 1.94 (95% confidence interval, 1.14–3.31). Results were driven by nonfatal events.

Conclusion—Heterozygous familial hypercholesterolemia relatives with an *LDLR* mutation had an increased long-term risk of adverse cardiovascular events. (*J Am Heart Assoc.* 2017;6:e005435. DOI: 10.1161/JAHA.116.005435.)

Key Words: coronary artery disease • epidemiology • genetics • heterozygous familial hypercholesterolemia • statins

Heterozygous familial hypercholesterolemia (heFH) is a common genetic disorder that, if untreated, is associated with a substantially increased risk of cardiovascular disease.^{1,2} The disease in its classic form is caused by low-density lipoprotein receptor (*LDLR*) mutations that are inherited in an autosomal-dominant pattern and affects at

least 1 in 250 people.^{3,4} Deleterious *LDLR* mutations result in decreased clearance of low-density lipoprotein cholesterol (LDL-C) from plasma and a subsequently elevated level of LDL-C.⁵

Prior to the introduction of statins in the early 1990s, the risk of premature coronary artery disease (CAD) among patients with clinically diagnosed heFH was substantially elevated.^{6,7} Although still at increased risk, studies have demonstrated that statins have substantially reduced this disease burden.^{7–10} Such studies, however, have focused primarily on heFH patients attending lipid clinics. The risk in these patients may not reflect the true risk of persons with an *LDLR* mutation because FH is widely underdiagnosed,¹¹ and patients may not be referred to lipid clinics unless LDL-C levels are very high or cardiovascular events have occurred—factors that may greatly influence the cardiovascular prognosis. Furthermore, screening of family members, even in lipid clinics, is often incomplete, making them underrepresented in such studies.¹² Consequently, we aimed to evaluate the long-term cardiovascular risk in

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This work was presented as a moderated Abstract Poster Presentation at the American College of Cardiology Annual Scientific Session, April 2–4, 2016, in Chicago, IL.

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Received December 27, 2016; accepted April 12, 2017.

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Clinical Perspective

What Is New?

- Heterozygous familial hypercholesterolemia relatives with *LDLR* mutation had an increased long-term risk of adverse cardiovascular events despite being in a statin era.

What Are the Clinical Implications?

- Our results support the importance of cascade screening and aggressive lipid-lowering therapy in families with familial hypercholesterolemia.

mutation-carrying heFH relatives recommended statin therapy compared with non-mutation-carrying heFH relatives and the general population.

Methods and Materials

Study Design and Cohorts

We conducted a cohort study of families with heFH identified between 1992 and 1994 through cascade screening. Patients (proband) with prevalent clinical FH in 1992 or new diagnoses of clinical FH during 1992–1993 were identified at the former Aarhus County Hospital Lipid Clinic (now Aarhus University Hospital). Clinical FH was defined as (1) a plasma level of total cholesterol >8.0 mmol/L (308.9 mg/dL), (2) LDL-C >6.0 mmol/L (231.7 mg/dL; if available), (3) the presence of tendinous xanthomata in the patient or in a first-degree relative, and (4) a family history of hypercholesterolemia. Probands identified were offered genetic testing as part of genetic studies on *LDLR* mutations.¹³ When an *LDLR* mutation consistent with a diagnosis of heFH was found, cascade screening of family members was performed. The mutation was followed as far as possible in the respective family pedigrees, thereby identifying mutation-carrying and noncarrying heFH relatives. These relatives made up the study cohort. None of the included heFH probands carried the apolipoprotein B R3500Q mutation causing familial-defective apolipoprotein B.

On study participation, a fasting blood sample was drawn from all participants. Pretreatment levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured, and LDL-C was calculated according to the Friedewald formula.¹⁴ Following the guidelines at that time, lipid-lowering treatment with statins was recommended to all mutation-carrying heFH participants at inclusion. Available statins at the time of initiation were lovastatin, pravastatin, and simvastatin.

A population-based comparison cohort from the general population was matched (10:1) to the family members by birth year and sex using the Danish Civil Registration

System.¹⁵ Controls were alive at the date the relative entered the database. Participants with heFH and controls with any outcome of interest (see below) registered before the date of inclusion were excluded.

Registries

In Denmark, the tax-supported healthcare system provides free unlimited access to public hospitals. This ensures registration of all hospital contacts. Linkage between Danish registries is possible using the Civil Personal Registration number, a unique identification number assigned to all Danish residents at birth or immigration.¹⁵ We were able to extract individual medical records on the heFH families and the control cohort from the Danish National Patient Registry (DNPR) and thereby to identify cardiovascular events.¹⁶ The DNPR contains records of all discharges from nonpsychiatric Danish hospitals since 1977 and from emergency room and outpatient clinics since 1995. In the DNPR, diagnoses are classified according to the eighth revision of the *International Classification of Diseases* until 1994 and the 10th revision thereafter, all coded by physicians. Furthermore, the registry contains all surgical procedures performed including cardiac revascularization procedures. Using the Danish Civil Registration System,¹⁵ we retrieved information on vital and migration status for each individual in the cohorts during the follow-up period. To assess compliance and adherence to guidelines for statin treatment in mutation-carrying heFH relatives, information on statin use (Anatomical Therapeutic Chemical code C10AA) were obtained through linkage with the Danish National Health Service Prescription Database,¹⁷ which contains data on all reimbursed prescriptions redeemed at Danish community pharmacies and hospital-based outpatient pharmacies since 2004.

Study Outcomes

Our primary end point was a composite of all-cause death and major adverse cardiovascular events including first events of acute myocardial infarction (AMI), ischemic stroke, transient ischemic attack, peripheral artery disease, or any coronary revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). As secondary outcomes, we assessed the individual components of the primary outcome separately as the composites of *coronary events* (AMI, PCI, and CABG), and *cardiovascular events* (AMI, stroke, transient ischemic attack, peripheral artery disease, PCI, and CABG).

Statistical Analysis

Baseline data are presented as numbers, proportions, and medians (interquartile ranges [IQRs]), as appropriate. Each

participant was followed from the individual date of inclusion to the date of first event, migration, death, or December 31, 2014, whichever came first. A median follow-up time was computed from age at inclusion. We computed 20-year cumulative incidence proportions of all individual outcomes (for nonfatal events, we considered death as a competing risk).¹⁸ The risk of the primary end point was graphically illustrated by the cumulative incidence function using the Kaplan–Meier estimator.

We used Cox proportional hazards regression models to compute crude and adjusted hazard ratios (HRs), with 95% confidence intervals (CIs), comparing the rate of the primary end point in the 2 groups of relatives (mutation-carrying and noncarrying heFH relatives) with a general population cohort as the reference. Furthermore, we compared the HR of the primary end point between the 2 groups of relatives. In the regression analyses, the estimates were adjusted for birth-year categories, and robust variance estimation was used to account for possible clustering effects within families. The proportional hazards assumptions were graphically assessed using log-log plots and were not found to be violated.

Finally, we evaluated the prevalence of primary statin prevention in the cohort after 2004 (when prescription data were available) by restricting to patients who were alive and without a cardiovascular event prior to January 1, 2004. In the same subcohort, we calculated the proportion of time in treatment as the number of statin tablets reimbursed during

follow-up after January 1, 2004, divided by the follow-up time in days in the same period for each patient.

All statistical analyses were performed using Stata software (StataSE v13.1). Because follow-up did not involve contact with patients or any intervention, patient consent and approval from an ethics committee was not required in Denmark. The study was approved by the Danish Data Protection Agency (record no. 2007-58-0010) and the Central Denmark Region (record no. 1-16-02-72-15).

Results

We included 220 relatives from 32 families and 2199 controls from the general population. Figure 1 shows the selection of study participants. The median age among relatives was 37 years (IQR: 27–52 years); 102 (46%) were men, and 118 (54%) had a deleterious *LDLR* mutation (Table 1). Median duration of follow-up was 21 years (IQR: 18–22 years), and total person-time at risk was 46 178 years. When evaluating the descriptive data on the use of statins, of the 92 mutation-carrying heFH relatives still at risk of a first-time event on January 1, 2004, 82 (89%) received statin treatment during their subsequent follow-up period. The median proportion of time in treatment was 77% (IQR: 33–99%). At baseline, however, none of the relatives were taking lipid-lowering medications.

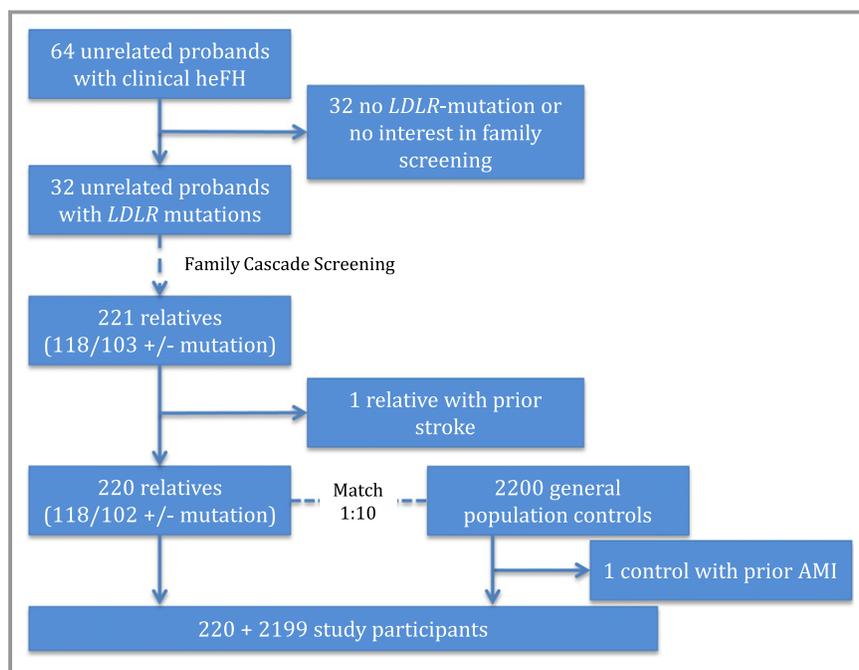


Figure 1. Flowchart showing the selection of study participants. AMI indicates acute myocardial infarction; heFH, heterozygous familial hypercholesterolemia; *LDLR*, low-density lipoprotein receptor.

Table 1. Baseline Characteristics for the Study Participants

	Mutation-Carrying heFH Relatives (n=118)	Non-Mutation-Carrying heFH Relatives (n=102)	General Population Comparison Cohort (n=2199)	Probands (n=32)
Sex				
Male	56 (47.5)	46 (45.1)	1019 (46.3)	14 (43.8)
Birth-year group, y				
Before 1930	13 (11.0)	11 (10.8)	240 (10.9)	8 (25.0)
1930–1939	17 (14.4)	12 (11.8)	290 (13.2)	6 (18.8)
1940–1949	13 (11.0)	16 (15.7)	289 (13.1)	7 (21.8)
1950–1959	24 (20.3)	23 (22.6)	470 (21.4)	5 (15.6)
1960–1969	28 (23.7)	21 (20.6)	490 (22.3)	6 (18.8)
After 1969	23 (19.5)	19 (18.6)	420 (19.1)	0 (0)
Median follow-up time (IQR)*	21 (13–22)	21 (19–22)	21 (18–22)	17 (5–22)
Verified <i>LDLR</i> mutation	118 (100)	32 (100)
Subtype of mutation				
Trp ⁶⁶ –Gly	24 (20.3)	3 (9.4)
Trp ²³ –Stop	19 (16.1)	7 (21.8)
Thr ³⁸³ –Pro	13 (11.0)	1 (3.1)
9-kb Deletion removing exon 3 to 6	10 (8.5)	1 (3.1)
5'-Splice donor G→A	9 (7.6)	3 (9.4)
3'-Splice acceptor G→A	9 (7.6)	3 (9.4)
2-kb Deletion removing exon 17	10 (8.5)	1 (3.1)
Others	24 (20.3)	13 (40.6)
Median blood levels, mmol/L (IQR)				
TC	9.64 (8.30–11.1) [†]	5.59 (4.93–6.58)	...	11.6 (10.2–12.4) [†]
HDL-C	1.13 (0.96–1.41)	1.31 (1.10–1.60)	...	1.28 (0.99–1.54)
LDL-C	7.75 (6.55–9.20) [‡]	3.50 (3.00–4.40)	...	9.45 (7.90–10.4) [‡]
Tg	1.31 (0.98–1.90)	1.20 (0.90–1.86)	...	1.20 (1.00–1.80)

Values are given in absolute numbers (percentages) unless otherwise stated. None of the relatives were taking lipid-lowering medications at baseline. All lipid levels were obtained at baseline. To convert blood levels to mg/dL, divide cholesterol levels by 0.0259 and Tg levels by 0.0113. HDL-C indicates high-density lipoprotein cholesterol; heFH, heterozygous familial hypercholesterolemia; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; TC, total cholesterol; Tg, triglycerides.

*Time from study inclusion until event of interest, migration, death, or December 31, 2014.

[†]Significant difference in TC and [‡]LDL-C between probands and mutation-carrying heFH relatives. Analyses performed by using the nonpaired, nonparametric Wilcoxon Mann–Whitney 2-sample test ($P<0.001$).

The cumulative incidence function of the primary end point is shown in Figure 2. Mutation-carrying heFH relatives had an increased 20-year risk of both coronary events and cardiovascular events overall compared with the non-mutation-carrying relatives and the general population cohort (Table 2).

The risk of the primary end point was higher in mutation-carrying heFH relatives compared with the general population (adjusted HR: 1.65; 95% CI, 1.17–2.33; Table 3). This was not the case in relatives without a mutation (adjusted HR: 0.85; 95% CI, 0.56–1.29). Accordingly, the risk in mutation-carrying heFH relatives compared with noncarrying relatives was increased (adjusted HR: 1.94; 95% CI, 1.14–3.31). Examining

the individual outcomes separately, the risks were higher in mutation-carrying heFH relatives compared with the general population for AMI (adjusted HR: 3.14; 95% CI, 1.78–5.55), transient ischemic attack (adjusted HR: 4.38; 95% CI, 1.95–9.84), PCI (adjusted HR: 4.78; 95% CI, 2.49–9.18) and CABG (adjusted HR: 13.8; 95% CI, 7.14–26.7). Risk of both coronary events and cardiovascular events were increased accordingly (Table 3). We observed no difference in any of the secondary outcomes among the noncarrying relatives compared with the general population cohort except for an elevated risk of coronary events. This was exclusively driven by cardiac revascularization procedures but not AMI (data not shown).

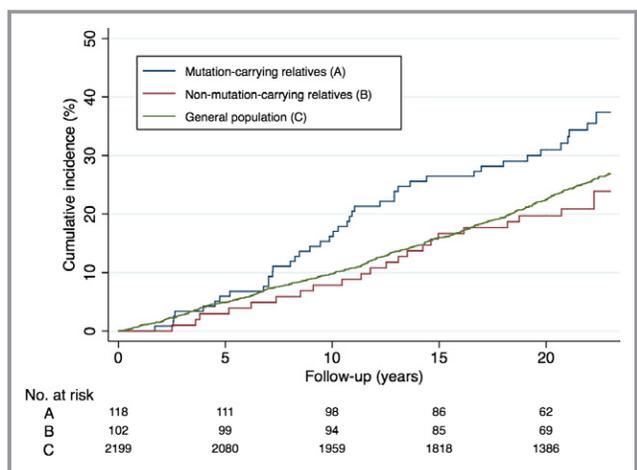


Figure 2. Cumulative incidence illustration of the primary end point in both groups of relatives and in the general population.

When comparing the 2 groups of relatives, only risk of coronary events, cardiovascular events, and CABG was elevated; however, a low number of events rendered separate outcome analyses inconclusive. We did not observe increased all-cause mortality in any of the groups of heFH relatives compared with the general population cohort.

Discussion

In this long-term follow-up study of relatives with molecular-genetic verified heFH who were recommended statin therapy from the time of diagnosis, we observed an elevated risk of adverse cardiovascular events in mutation-carrying relatives compared with the general population. The risk was driven by an increased risk of coronary events, whereas the mortality in heFH relatives was not substantially different from that of the general population.

In 1974, Stone et al reported a significantly elevated cardiovascular risk in relatives of patients with clinically diagnosed heFH compared with healthy relatives.⁶ The cumulative incidence proportions of fatal and nonfatal CAD at 60 years were 52% and 32% in mutation-carrying male and female participants, respectively. At that time, technology did not allow for information on mutation status, and the definition of the outcomes relied largely on symptoms and ECG findings, which may complicate direct comparisons with our findings. The much-lower cumulative incidence proportions in the present study, however, may indicate much-improved lipid-lowering treatment in later years and a markedly improved prognosis for mutation-carrying relatives over time.

The risk of cardiovascular disease in heFH patients from lipid clinics has been investigated previously.⁸ A prospective Dutch study followed 261 FH patients from 1990 and found a

Table 2. Twenty-Year Cumulative Risk for Separate and Combined Secondary Outcomes in Mutation-Carrying- and Noncarrying heFH Relatives and in the General Population*

	Participants, n (Total)	Events	20-Year Cumulative Incidence (95% CI)
Coronary event[†]			
General population	2199	93	4% (4–5)
Mutation-carrying heFH relatives	118	27	23% (16–31)
Noncarrying heFH relatives	102	10	12% (5–21)
Cardiovascular event[‡]			
General population	2199	207	10% (8–11)
Mutation-carrying heFH relatives	118	28	24% (17–32)
Noncarrying heFH relatives	102	14	14% (8–21)
AMI			
General population	2199	79	4% (3–5)
Mutation-carrying heFH relatives	118	14	12% (7–19)
Noncarrying heFH relatives	102	5	7% (2–16)
Stroke			
General population	2199	97	5% (4–5)
Mutation-carrying heFH relatives	118	7	6% (3–12)
Noncarrying heFH relatives	102	8	8% (4–14)
PCI			
General population	2199	46	2% (1–3)
Mutation-carrying heFH relatives	118	12	10% (6–17)
Non-carrying heFH relatives	102	5	5% (2–10)
CABG			
General population	2199	24	1% (1–2)
Mutation-carrying heFH relatives	118	14	12% (7–19)
Noncarrying heFH relatives	102	4	4% (1–9)

Cumulative incidence results for transient ischemic attack and peripheral artery disease have been removed given cell sizes of <4 events and thus to reduce identifiability of individuals in data. AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CI, confidence interval; heFH, heterozygous familial hypercholesterolemia; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

*All estimates are crude but accounted for death as a competing risk.

[†]Included AMI, PCI and CABG.

[‡]Included AMI, stroke, transient ischemic attack, peripheral artery disease, PCI, and CABG.

8.7 times higher risk of AMI in untreated heFH patients compared with the general population. In contrast, it was not certain whether the risk of AMI was increased in heFH patients receiving primary preventive statin treatment (HR:

Table 3. Incidence Rates and Hazard Ratios in Mutation-Carrying- and Noncarrying heFH Relatives Compared With General Population and the 2 Groups of Relatives Compared With Each Other

Exposure of Interest	Number of Events	Incidence Rate Per 1000 Person-Years (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
Primary end point				
General population (reference)	549	13.1 (12.0–14.2)	1.00	1.00
Mutation-carrying heFH relatives	41	19.4 (14.3–26.3)	1.50 (1.09–2.07)	1.65 (1.17–2.33)
Noncarrying heFH relatives	23	11.0 (7.24–16.7)	0.84 (0.55–1.29)	0.85 (0.56–1.29)
Comparison of relatives [†]	1.78 (1.06–3.00)	1.94 (1.14–3.31)
All-cause mortality				
General population (reference)	430	9.89 (9.00–10.9)	1.00	1.00
Mutation-carrying heFH relatives	18	7.40 (4.66–11.7)	0.74 (0.47–1.18)	0.71 (0.46–1.09)
Noncarrying heFH relatives	13	6.20 (3.60–10.7)	0.62 (0.36–1.09)	0.57 (0.33–1.00)
Comparison of relatives [†]	1.19 (0.58–2.42)	1.23 (0.62–2.46)
Coronary event[‡]				
General population (reference)	104	2.43 (2.00–2.94)	1.00	1.00
Mutation-carrying heFH relatives	28	13.1 (9.04–19.0)	5.43 (3.57–8.27)	5.91 (3.83–9.10)
Noncarrying heFH relatives	10	4.95 (2.66–9.21)	2.05 (1.07–3.92)	2.06 (1.07–3.98)
Comparison of relatives [†]	2.66 (1.29–5.49)	2.86 (1.37–5.99)
Cardiovascular event[§]				
General population (reference)	228	5.42 (4.76–6.17)	1.00	1.00
Mutation-carrying heFH relatives	31	14.7 (10.3–20.8)	2.74 (1.88–4.01)	3.01 (2.02–4.48)
Noncarrying heFH relatives	15	7.50 (4.52–12.4)	1.38 (0.82–2.33)	1.39 (0.83–2.33)
Comparison of relatives [†]	1.98 (1.07–3.68)	2.16 (1.16–4.04)

AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CI, confidence interval; heFH, heterozygous familial hypercholesterolemia; PCI, percutaneous coronary intervention.

*Hazard ratios adjusted for birth-year categories.

[†]Cox regression comparison of the 2 groups of relatives with non-mutation-carrying heFH relatives as reference.

[‡]Included AMI, PCI, and CABG.

[§]Included AMI, stroke, transient ischemic attack, peripheral artery disease, PCI, and CABG.

1.44; 95% CI, 0.80–2.60).⁸ The continuing excess risk, even among treated mutation-carrying heFH relatives, seems to be confirmed in the present study.

Despite an increased risk of cardiovascular events, we did not observe an increase in all-cause mortality among mutation-carrying heFH relatives. This is in contrast to a Dutch study of 214 heFH patients from lipid clinics in primary prevention therapy with statins. That study observed an overall 2.6-fold increased mortality from CAD compared with the general population that was markedly higher (7.6-fold increased risk) in younger patients aged 40 to 59 years.¹⁹ A larger study, however, included 2582 heFH patients free of CAD and attending lipid clinics in the United Kingdom.⁷ The authors found a 48% reduction in CAD mortality in the period after the introduction of statins (after 1992) compared with before. This resulted in all-cause mortality that was actually lower than that of the general population. Although cardiovascular morbidity was not

addressed, the findings of lower mortality among heFH patients in lipid clinics are consistent with those observed among mutation-carrying heFH relatives in the present study. It is conceivable that the absence of increased mortality in mutation-carrying heFH relatives can be explained by statin therapy and the overall improvements in CAD treatment, but it might simply be due to chance, as the number of deaths in the cohort was relatively low.

Our analyses of prescription data suggest a high degree of statin use in relatives with heFH. Nevertheless, these patients still display an elevated risk of cardiovascular disease compared with the general Danish population. A possible explanation could be not reaching guideline-based LDL-C targets. A Norwegian study found that >50% of patients diagnosed with an *LDLR* mutation or familial-defective apolipoprotein B-100 were considered inadequately treated despite 82% being on lipid-lowering medication.²⁰ Another likely explanation may relate to the lifelong burden of high

LDL-C. Even though heFH patients are treated with statins from adulthood and may reach normal LDL-C levels from statin-treatment initiation, several years of exposure to high cholesterol levels may lead to increased cardiovascular disease risk. This hypothesis is supported by observations from genetic studies in which polymorphisms causing modestly lower LDL-C levels confer a CAD risk reduction that is markedly higher than similar LDL-C reductions obtained in randomized controlled trials of statins.²¹ This result is likely caused by a lifelong lower LDL-C level obtained by such polymorphisms as opposed to the short period of a lower LDL-C level obtained in statin trials. In addition, randomized trials in children with heFH suggest that very early initiation of statin treatment leads to regression of carotid atherosclerosis, a marker of increased cardiovascular risk.^{22,23} Whether heFH relatives treated with statins from early childhood would obtain a cardiovascular risk similar to that of the general population remains unanswered.

Strengths and Limitations

The main strengths of our study include the genetically verified heFH diagnoses and the almost complete follow-up for cardiovascular events and death over a period of >20 years. The validity of the diagnosis codes used in our study is generally high, and the positive predictive values of the diagnoses in DNPR have been estimated at $\approx 97\%$ for AMI,²⁴ 97% for ischemic stroke,²⁵ 69% for transient ischemic attack,²⁵ 91% for peripheral artery disease,²⁴ 98% for PCI,²⁶ and 96% for CABG.²⁶ By collecting data from independent medical registries, we avoided reliance on self-reporting.

Some limitations deserve mention. The sample size of the relatives was relatively small, reducing the precision of estimates of secondary outcomes. We did not have data on redeemed prescriptions before 2004 and thus could not identify ongoing statin treatment before 2004; therefore, we may have overestimated the prevalence of primary statin prevention because relatives with cardiovascular events before 2004, on average, may be less compliant than those alive and without events in 2004. Prescription data were included as descriptive numbers only and not as a covariable in consideration of immortal time bias.²⁷ We did not possess information on cardiovascular risk factors such as blood pressure, smoking habits, or other lifestyle factors. Because mutation-carrying heFH relatives were informed of their carrier status, such individuals might potentially adhere to a healthier lifestyle because of the awareness of increased cardiovascular risk. This would bias our results toward underestimation of the true effect of carrying an LDLR mutation.²⁸ In addition, we did not measure LDL-C levels during follow-up; therefore, we do not know whether LDL-C targets were actually achieved.

Conclusion

HeFH relatives with *LDLR* mutations had an increased long-term risk of adverse cardiovascular events.

Sources of Funding

Amgen has provided an unrestricted grant for the study (Jensen). The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosures

None.

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J Am Heart Assoc. 2017;6:e005435; originally published June 26, 2017;
doi: 10.1161/JAHA.116.005435

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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