

2.5-fold increased risk of recurrent acute myocardial infarction with familial hypercholesterolemia

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ABSTRACT

Background and aims: A first-time acute myocardial infarction (AMI) is a severe diagnosis that leads to initiation or intensification of lipid-lowering medication to prevent recurrent events. Individuals with familial hypercholesterolemia (FH) already use high-intensity lipid-lowering medication at the time of an incident AMI due to their diagnosis. Hence, we hypothesized that compared with matched non-FH controls, individuals with genetically verified FH have increased mortality and risk of recurrent AMI after their first event.

Methods: The study population comprised 4871 persons with genetically verified FH, and 96,251 age and sex matched controls randomly selected from the Norwegian population. Data were obtained from the Cardiovascular Disease in Norway Project, the Norwegian Patient Registry and the Norwegian Cause of Death Registry. Incidence of AMI, all-cause mortality and recurrent AMI after incident AMI were analyzed for the period 2001–2017. Incidence and mortality were compared using hazard ratios (HR) from Cox regression. Risk of recurrent AMI was compared using sub-hazard ratios (SHR) from competing risk regression with death as a competing event.

Results: We identified 232 individuals with FH and 2118 controls with an incident AMI [HR 2.10 (95% CI 1.83–2.41)]. Among survivors ≥ 29 days after the incident AMI, both mortality [HR = 1.45 (95% CI: 1.07–1.95)] and recurrent AMI [SHR = 2.53 (95% CI: 1.88–3.41)] were significantly increased among individuals with FH compared with non-FH controls.

Conclusions: Individuals with FH have increased mortality and increased risk of recurrent AMI after the first AMI event compared with controls. These findings call for intensive follow-up of individuals with FH following an AMI.

1. Introduction

Familial hypercholesterolemia (FH) is an inherited disorder estimated to affect an average of 1:300 [1]. FH is usually caused by a mutation in the low-density lipoprotein (LDL) receptor gene resulting in high circulating levels of LDL-cholesterol (LDL-C) from birth [2,3]. Ideal treatment in FH includes lifelong lipid-lowering treatment [4] and observational data on statin therapy initiated in childhood has shown to

slow the progression of atherosclerosis and reduce the risk of coronary heart disease (CHD) after 20 years of follow-up [5]. Individuals with genetically verified FH have increased risk of suffering from an early incident acute myocardial infarction (AMI) event or premature death compared with the general population [6]. After the first AMI, individuals with possible or probable FH have increased risk of combined cardiovascular disease (CVD) endpoint (death, AMI or stroke) or recurrent AMI after ≤ 5 years of follow-up [7,8]. However, as CVDs differ

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in severity and treatment, risk of mortality and recurrent AMI after the first event should be analyzed separately from other CVDs. With the present study, we aimed to strengthen existing findings by comparing the risk of incident and recurrent AMI and mortality after the incident AMI between individuals with genetically verified FH and age and sex matched controls during 2001–2017.

2. Materials and methods

2.1. Study population

This is a prospective matched cohort study comprising individuals with genetically verified FH and age and sex matched non-FH controls obtained from the general population. The FH population was obtained from the Unit for Cardiac and Cardiovascular Genetics (UCCG) database at Oslo University Hospital, where all individuals with FH are included after genetic diagnosis and after obtaining written informed consent [3, 10]. In Norway, the majority of individuals with genetically verified FH are identified through cascade screening, meaning that the relatives of an index patient are tested for different FH mutations [3, 10].

In the present study, we included a cohort of 5635 individuals who were genetically diagnosed with FH between January 1, 1992 and March 1, 2014 (deadline of inclusion to the main study). Of these, we were missing exact inclusion date and hence the date of genetically verified FH diagnosis in 744 individuals who were diagnosed prior to 1992. These individuals were assigned the inclusion date January 1, 1992, as previously described [10]. For each individual with FH, 20 controls living in Norway in the same time period were matched according to sex and age, yielding a non-FH control sample of 112,589 individuals. This inclusion of a matched control sample was performed as an overall goal to study risk of several diseases including cancer [10]. In the present study, we excluded 764 individuals with FH and 16,338

controls who either had been hospitalized with AMI or were deceased before study start or who were <20 years of age before study end (December 31, 2017). For the control cohort, we also excluded those who, after exclusion of individuals in the FH population, were no longer matched to an individual with FH. Hence, the final sample for analysis of incident AMI consisted of 4871 individuals with FH and 96,251 age and sex matched controls (Fig. 1).

During the follow-up time 2001–2017, out of 232 cases of incident AMI in the FH cohort and 2118 in the control cohort, 221 and 1947 cases (no longer matched) were hospitalized with AMI and were included for analysis of mortality, whereas risk of recurrent AMI was investigated in 190 and 1666 survivors, respectively, who were still alive ≥ 29 days after discharge from incident AMI hospitalization (Fig. 1).

2.2. Registry linkages

Information on incident and recurrent AMI and mortality after AMI from 2001 through 2017 was obtained by linking each individual's unique personal identification number to the following databases and registries: The Cardiovascular Disease in Norway Project (CVDNOR) at the University of Bergen (hospitalization data from 1994 through 2007) [11, 12], the Norwegian Patient Registry (hospitalization data from 2008 through 2017), and the Norwegian Cause of Death Registry (date and cause of death from 1992 through 2017) (Fig. 2). Endpoints were defined according to the International Classification of Diseases (ICD), version 9 (ICD-9) and version 10 (ICD-10). An incident case of AMI was defined as a hospitalization with AMI (ICD-9: 410, ICD-10: I21, I22) as main or secondary discharge diagnosis, or as the underlying cause of death without prior AMI events.

As illustrated in Fig. 2, in order to allow at least 7 years of look-back for previous events, we used data for the period 1994–2000 as washout, and analyzed incidence of AMI [13] for the period 2001–2017. Within

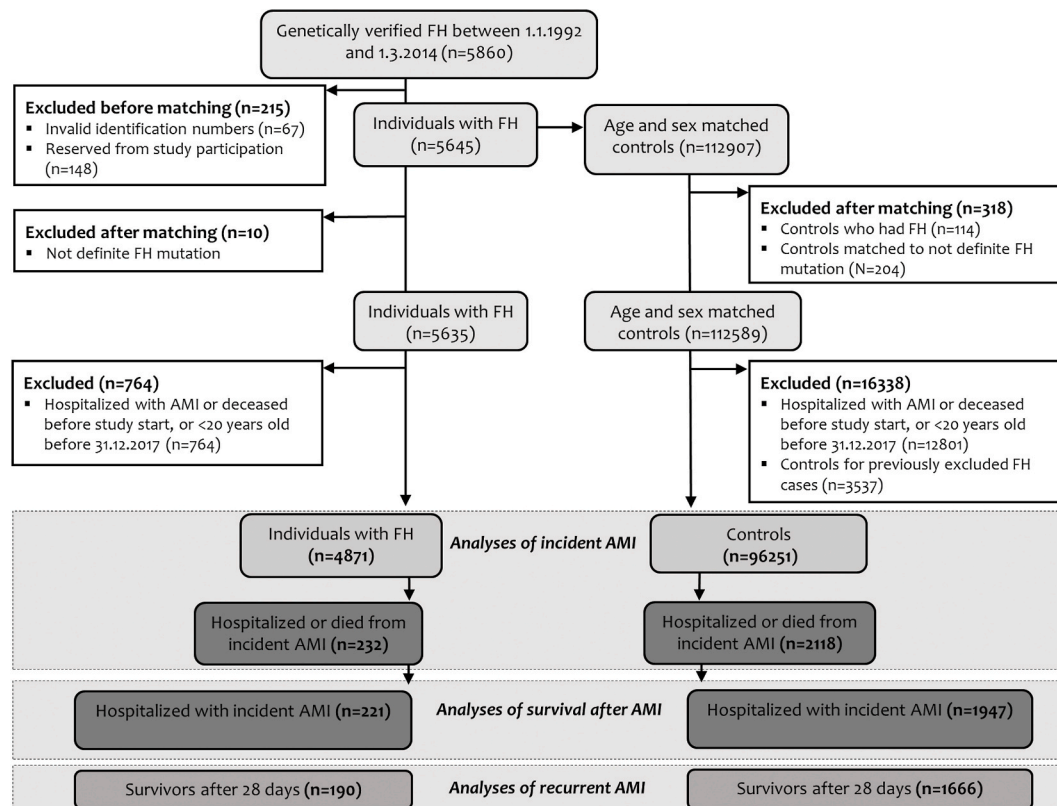


Fig. 1. Flow chart of inclusion and exclusion of individuals in the main study and individuals available for analysis of incidence, mortality and re-hospitalization of AMI in FH and controls.

AMI, acute myocardial infarction; FH, familial hypercholesterolemia.



Fig. 2. Individuals with FH registered in the Unit for Cardiac and Cardiovascular Genetics Registry between 1992 and 2014 were obtained through registry linkage from 1992 through 2017.

In order to have at least 7 years of washout for previous events prior to start of follow-up for everyone, we analyzed incidence of AMI for the period 2001–2017. AMI, acute myocardial infarction; FH, familial hypercholesterolemia; CVDNOR, The Cardiovascular Disease in Norway Project; NPR, The Norwegian Patient Registry.

each case set, the start of follow-up was defined as the latest date of the following three dates: the registration date in the UCCG Registry for the FH diagnosis, January 01 in the year the person reached age 20, or January 01, 2001. All individuals were followed until their first AMI, death or December 31, 2017 (study end), whichever occurred first.

2.3. Mortality

In analyses of all-cause mortality after AMI, we included individuals who were hospitalized with an incident AMI. Follow-up was measured from the date of hospitalization until death or December 31, 2017, whichever occurred first. We further split the follow-up period into short-term (0–28 days) and long-term (≥ 29 days) mortality among survivors.

2.4. Recurrent acute myocardial infarction

Recurrent AMI was calculated as time from day 29 after discharge of incident AMI and until a new hospitalization with AMI as primary or secondary diagnosis, death, or December 31, 2017, whichever occurred first. Any re-hospitalizations of AMI occurring 0–28 days after incident AMI were considered part of the initial AMI and not a new event.

2.5. Approvals

The Regional Committee of Medical and Health Research Ethics South-Eastern Norway approved the study (reference 2011/1343 REK Sør-Øst B). The study was granted exemption from the obligation to obtain informed consent, as previously described [10]. The study complies with the Declaration of Helsinki and was reported to the Norwegian Data Protection Official at Oslo University Hospital.

2.6. Statistics

Incidence of AMI was compared between individuals with FH and the controls using cumulative incidence plots obtained using the *stcompet*-package in Stata with age as the time scale and hazard ratios (HR) from Cox proportional hazards regression. We also performed Fine & Gray competing risk regression with death from other causes than AMI treated as competing events, which yielded similar results. We therefore chose to only present HRs from Cox regression in analyses of incidence of AMI. All-cause mortality among individuals hospitalized for incident AMI (the FH and control populations were no longer matched) was analyzed using Cox regression with follow-up measured from the date of

hospitalization until death or December 31, 2017, whichever occurred first. Results were split into short-term and long-term mortality rates among survivors on day 28. HRs in main analyses were adjusted for age and sex. In additional analyses, we also adjusted for comorbidities (heart failure, atrial fibrillation, hypertension, diabetes and stroke) reported during the incident AMI hospitalization. Among the survivors, risk of recurrent AMI was analyzed using competing risk regression with death treated as competing event and reported as sub-hazard ratios (SHR), adjusted for age. All results were stratified on sex, and all analyses were performed with Stata version 15.

3. Results

The sex distribution in the initial matched study populations was 47% men and 53% women, with a mean age at start of follow-up for analysis of incident AMI of 38.4 ± 15.9 years in FH and 38.1 ± 15.7 years in controls.

In total, 232 cases of incident AMI were registered in the FH population and 2118 cases in the control population. The FH population had a 2-fold increased risk of incident AMI compared with controls [HR 2.10 (95% CI: 1.83–2.41)] with similar excess risk in men [HR 2.20 (95% CI: 1.85–2.61)] and women [HR 1.95 (95% CI: 1.55–2.44)]. The cumulative incidences of AMI in the FH population were higher than in the control population for both men and women in all ages as illustrated in Fig. 3. Among those with incident AMI, 221 in the FH population and 1947 controls were hospitalized for AMI, with a mean age at hospitalization of 60.5 ± 15.4 years in FH, and 65.3 ± 12.4 years in controls.

3.1. Mortality

Among the 221 and 1947 individuals hospitalized with AMI, 63 individuals (28.5%) with FH and 531 controls (27.2%) died during the follow-up period (2001–2017), yielding a HR of 1.32 (95% CI: 1.01–1.71), adjusted for age and sex. The excess mortality was higher in men with FH [HR adjusted for age 1.44 (95% CI 1.0–2.07)] whereas the corresponding age-adjusted HR in women was 1.20 (95% CI 0.81–1.76).

After further adjustment for comorbidities reported during the incident AMI hospitalization (heart failure, atrial fibrillation, hypertension, diabetes and stroke), the HR for the total population was reduced to 1.27 (95% CI: 0.98–1.65). The main cause of death was CHD in both groups; 34.5% in the FH population and 32.6% in controls.

As shown in Fig. 4, the increased mortality in the FH population was present in the long-term (≥ 29 days) and not significantly different in the

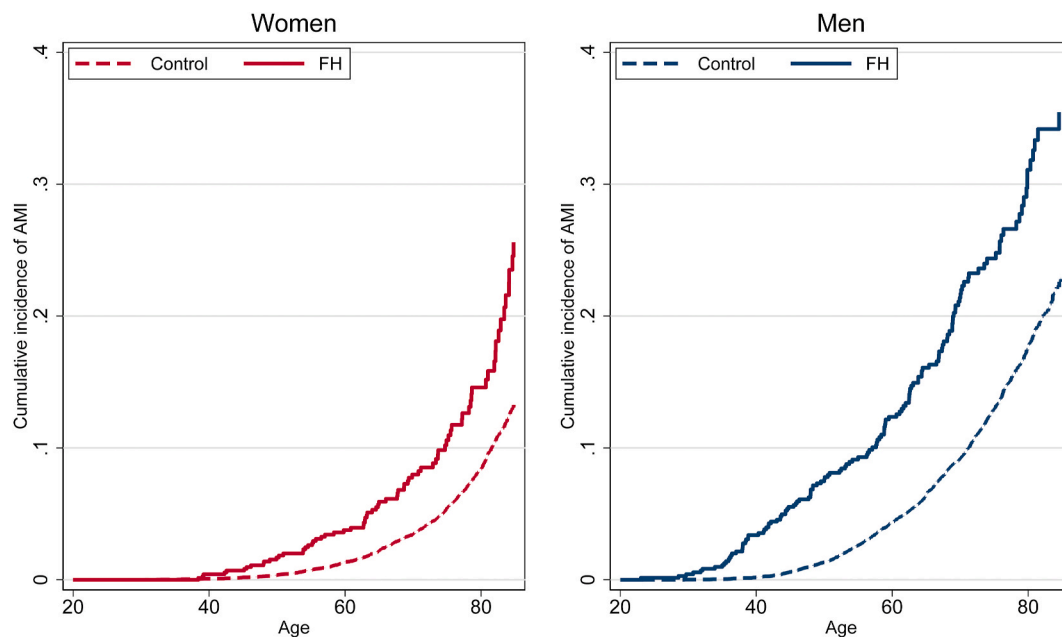


Fig. 3. Cumulative incidence of acute myocardial infarction (AMI) during 2001–2017 for the familial hypercholesterolemia (FH) cohort and the control cohort with age as the timescale.

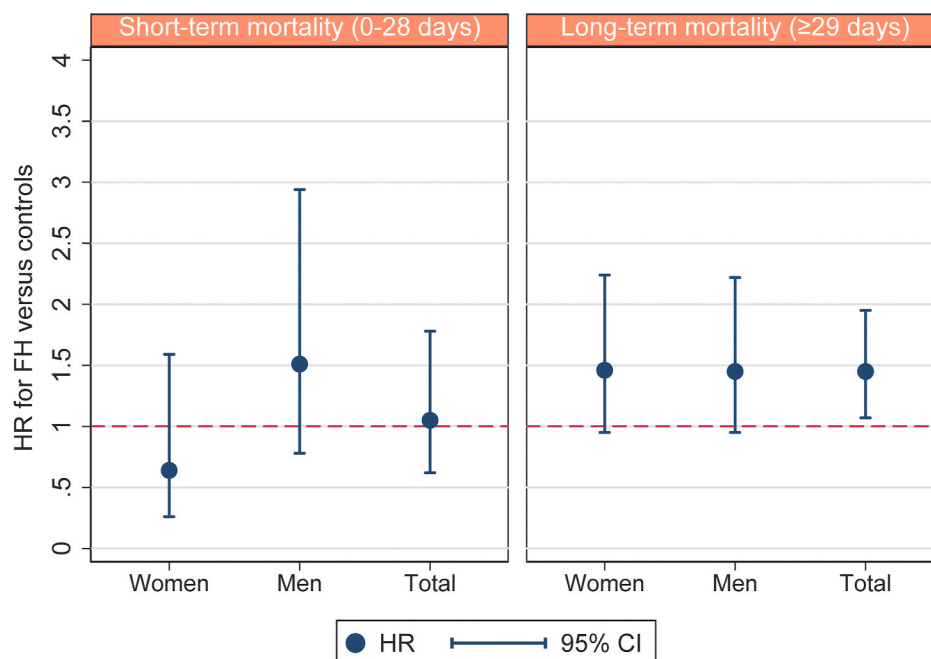


Fig. 4. Risk of short-term (0–28 days) and long-term mortality (≥ 29 days) after incident AMI presented as age adjusted HR in individuals with FH versus controls. AMI, acute myocardial infarction; FH, familial hypercholesterolemia. HR; hazard ratio.

short-term (0–28 days) follow-up after hospitalization with incident AMI.

Twenty-nine or more days after being hospitalized with incident AMI, the FH population had a 45% increased mortality compared with controls [age and sex adjusted HR 1.45 (95% CI: 1.07–1.95)], with similar increased risk among men and women with FH. After further adjustment for the comorbidities reported during hospitalization, the excess mortality in FH was reduced, but it was still significantly higher than in controls [HR 1.38 (95% CI: 1.02–1.86)].

3.2. Recurrence of acute myocardial infarction

In total, 30% ($n = 57$) of those who survived the first 28 days after discharge for incident AMI in the FH population were re-hospitalized with recurrent AMI after ≥ 29 days during the follow-up period. In comparison, only 15% ($n = 248$) of non-FH controls experienced a recurrent AMI during the same period. These numbers correspond to a 2.5-fold increased risk of recurrent AMI among individuals with FH compared with controls [SHR 2.53 (95% CI: 1.88–3.41)] after adjustment for age and sex. Further adjustment for comorbidities reported during the hospitalization for incident AMI did not reduce the increased

risk [SHR 2.63 (95% CI: 1.95–3.54)]. This increased risk in FH was similar among men and women with FH (Table 1).

4. Discussion

In this large prospective cohort study, we found that after an incident AMI, the long-term mortality was increased by 45%, and the risk of recurrent AMI was 2.5-fold increased during 17 years of follow-up in individuals with genetically verified FH compared with controls.

These results in 232 individuals with genetically verified FH who had experienced a first-time AMI support and extend (with 17 years of follow-up) previous results in individuals with probable FH [7,8,14–19]. Rerup and co-workers found that individuals with probable FH had a 1.28-fold increased risk of recurrent AMI after a median of 3.3 years of follow-up [8], whereas Danchin and co-workers found a 2.2-fold increased risk of the combined outcome death or recurrent major cardiovascular events after 5 years of follow-up in probable FH [7]. Several other studies also report increased risk of recurrent CVD in individuals with clinical/possible FH compared with non-FH individuals with a follow-up time of at least one year [14–19]. However, it should be noted that due to their diagnosis, individuals with FH are more likely to have been frequently followed up by their general physicians and at lipid clinics compared with controls. Increased risk of hospitalization with less acute CVD diagnoses among individuals with FH after an incident AMI could therefore reflect increased follow-up and treatment. This kind of treatment bias cannot explain the observed increased risk of recurrent acute events like AMI reported in the present study. Furthermore, classifying FH according to the Simone Broome Register criteria [18], the definition by the American Heart Association [17] and the Dutch Lipid Clinic definition [19] yield different prevalence of FH, and accordingly less comparable risk estimates. Our results on genetically verified FH are therefore needed to verify previous findings.

The increased risk of recurrent AMI in FH is observed in a time period with widespread use of statins among individuals with genetically verified FH [20,21]. We did not have information on the use of lipid-lowering medication in the present study. However, it is reasonable to assume that most of the individuals with FH already used lipid-lowering medication when experiencing their first-time AMI, since all had been genetically diagnosed at the start of follow-up. In a study of Norwegian individuals with FH by Bogsrud and co-workers, 89% of those visiting lipid clinics were prescribed statins, and in those at high risk, the prevalence was 93% [20]. A recent Norwegian study demonstrated that among young individuals (<45 years) hospitalized with AMI, statins were reported to be used by 63% among those who had FH and 29% of those without FH at admission [22]. After an incident AMI, the statin dose in most individuals with FH will be increased if they are not already using potent statins. However, intensifying the dose or type of statins only reduces LDL-C levels to a certain extent, as demonstrated in a subpopulation of the current population where the LDL-C treatment goal was only achieved by 25% of the subjects with FH at normal risk,

and 8% with very high risk [20]. Hence, little can be done to further reduce AMI risk and LDL-C levels in individuals with FH without add-on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Accordingly, with little or no further reduction post AMI, the mean on-treatment LDL-C level in individuals with FH would remain at 3–4 mmol/L despite receiving a maximally accepted dose of statin therapy with or without ezetimibe [20,23]. On the other hand, individuals without FH, who mostly have not received statins before their incident AMI [22], will be prescribed potent statins immediately after AMI, which would reduce their LDL-C levels significantly [4,24]. In this way, the controls in this study would have a major reduction in their LDL-C levels following the incident AMI, whereas the FH population would have little (or no) change in their LDL-C levels. In sum, this is likely to have impact on the increased risk of recurrent AMI and mortality seen in the FH population.

Different lifestyle factors such as smoking and poor diet are known risk factors for CVD [4]. The Norwegian FH population is, however, characterized by fewer smokers and healthier lifestyle and diet than non-FH individuals [25], as also discussed in our recent publication on cancer risk in the same cohort of individuals with FH [10]. In the present study, we do not know the smoking prevalence in those who experienced an AMI, but the previous publications from the same FH cohort [4,25] suggest that smoking and other lifestyle factors are less likely to have contributed to the increased risk of recurrent AMI seen in this FH population here. On the contrary, if we had been able to adjust for smoking in the analyses, the data suggest that the HR could have been even higher.

Several other primary CVD risk factors might have contributed to the increased risk in FH observed post AMI [6,26]. Diabetes increases the risk of death or recurrent AMI after the first event [27,28]. However, among the hospitalized cases in this study, the proportions with diabetes and hypertension at the time of the incident AMI were non-significantly lower among individuals with FH compared with controls, and the proportions with heart failure, atrial fibrillation and stroke were similar among individuals with and without FH (Supplementary file 1). Furthermore, adjusting for the comorbidities did not significantly impact the mortality rate nor the risk of recurrent AMI, and our findings therefore suggest that the higher mortality rate and risk of recurrent AMI in this FH population after incident AMI cannot be explained by a higher level of some of the most important comorbidities at the time of incident AMI. We cannot however rule out that individuals with FH have a poorer health status or experience a more severe first-time AMI than non-FH individuals which again could have impacted their increased risk of mortality and recurrent AMI. Unfortunately, we did not have data on indicators of severity of AMI in this study. Still, for men we did observe a HR for short-term mortality of 1.51 (95% CI: 0.95–2.22), which could indicate increased mortality in the acute phase in men. However, the result was not significant, and has to be interpreted with caution.

Not surprisingly, the doubled risk of incident AMI in individuals with genetically verified FH compared with age and sex matched controls

Table 1

Re-hospitalization with acute myocardial infarction (AMI) among those who survived the first 28 days after an incident AMI hospitalization during 2001–2017, in a population with familial hypercholesterolemia (FH) versus controls.

	Survivors to day 28	Re-hospitalizations after day 28	Person-years in 1000	Incidence rate per 1000 person years (95% CI)	SHR re-hospitalization (95% CI) ^a
Total study population					
Controls	1666	248	8.1	30.5 (26.9–34.5)	1
FH	190	57	0.8	69.4 (53.5–90.0)	2.53 (1.88–3.41)
Women					
Controls	616	98	2.8	34.8 (28.6–42.5)	1
FH	67	19	0.3	68.9 (43.9–108.0)	2.24 (1.35–3.69)
Men					
Controls	1050	150	5.3	28.2 (24.0–33.1)	1
FH	123	38	0.6	69.7 (50.7–95.7)	2.68 (1.85–3.87)

^a Sub hazard ratio (SHR) from competing risk regression. 95% CI; 95% confidence interval. FH; familial hypercholesterolemia. AMI; acute myocardial infarction.

from 2001 through 2017, supports and extends previous findings [6,21]. However, with respect to the large number of undiagnosed individuals with FH, this is of concern. Only 1/3 of those estimated to have FH in Norway have currently been diagnosed [29], and the risk of incident AMI in non-diagnosed and untreated individuals with FH is likely to be considerably higher. This is illustrated by the recent finding that among young (<45 years) individuals hospitalized with AMI, 3% of the total population (or 21% of those actually tested) had genetically verified FH [22]. Taken together, our results suggest that the severity and consequences of having an FH diagnosis (and probably with an insufficient treatment of individuals with FH) are likely to have impacted on the increased risk of incident and recurrent AMI, in addition to the increased mortality in individuals with FH, compared with non-FH controls.

There are several strengths of the study. First, all individuals with FH included in the study have genetically verified FH, obtained from one of the largest national FH cohorts in the world [3,9]. The study includes 20 controls per individual with FH who were matched on age and sex, and the follow-up time is long (2001–2017 with additional 7 years of wash-out). FH is inherited from heterozygous parents across socioeconomic strata. Therefore, there is no need to adjust for socioeconomic status. We obtained the endpoints from national population-based registries with a long follow-up time, which ensures an almost complete follow-up. Information on date and cause of death made it possible to consider death as a competing event in analyses of risk of incident and recurrent AMI.

Limitations include the lack of details on lifestyle, biochemical measures of LDL-C and other risk factors, smoking history and use of lipid-lowering medication. Furthermore, the matching of controls to the FH population was performed with the aim of studying the risk of incident AMI. Since individuals with FH experience their first AMI at a younger age compared with controls, the two groups were not matched in analyses of survival after AMI and risk of recurrence. To account for this, we adjusted for age and sex, and also for various comorbidities in additional analyses. There could be other important unmeasured differences between the individuals with FH and controls at the time of incident AMI. We cannot rule out that the observed increased risk of re-hospitalization could at least partly be caused by other factors than an FH mutation. In addition to the matching, there might also be unknown selection bias towards the population being studied because the current sample does not necessarily reflect the total population of individuals with FH in Norway due to the possible high number of undiagnosed individuals with FH [29]. The lack of active consent and hence the low reservation rate to the present study (2.5%) [10], however, strengthens the generalizability of the results.

In summary, our results demonstrate that during 17 years of follow-up, individuals with genetically verified FH have a more than doubled risk of both incident and recurrent AMI and increased mortality compared with non-FH controls. These findings therefore demonstrate a poorer prognosis after incident AMI in individuals with FH, underscoring the severity of the FH diagnosis and the need to monitor individuals with FH (even more) closely after their first AMI.

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Declaration of competing interest

H.W.K., J.I., L.J.M., G.S.T. and T.L. declare no competing interests. K. S. has received personal fees from MedXplore, outside the submitted work. M.P.B. reports personal fees from Amgen, Sanofi-Aventis, Bristol-Myers Squibb and grants from Kaneka, Mills DA, outside the submitted work. K.B.H. reports grants from Tine SA, Mills DA, Olympic Seafood, Kaneka grants and personal fees from Amgen, Sanofi, and personal fees

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Author contributions

K.S., H.W.K., K.R., J.I., L.J.M., M.P.B., K.B.H. & T.P.L. contributed to the conceptualization of the study. K.S., H.W.K., K.R., J.I. were responsible for project administration. J.I., G.S.T. and T.P.L. were responsible for data curation and J.I. for analysis. K.S., H.W.K., J.I., K.R. wrote the original draft. All authors reviewed, edited and approved the final manuscript.

CRediT authorship contribution statement

Karianne Svendsen: Conceptualization, Project administration, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, were responsible for project administration, All authors reviewed, edited and approved the final manuscript. **Henriette W. Krogh:** Conceptualization, Project administration, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, were responsible for project administration, All authors reviewed, edited and approved the final manuscript. K.R., contributed to the conceptualization of the study, were responsible for project administration, wrote the original draft. All authors reviewed, edited and approved the final manuscript. **Jannicke Igland:** Conceptualization, Project administration, Data curation, Formal analysis, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, were responsible for project administration, were responsible for data curation, analysis, wrote the original draft. All authors reviewed, edited and approved the final manuscript. **Grethe S. Tell:** Data curation, Writing – review & editing, Writing – original draft, were responsible for data curation, All authors reviewed, edited and approved the final manuscript. **Liv J. Mundal:** Conceptualization, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, All authors reviewed, edited and approved the final manuscript. **Kirsten B. Holven:** Conceptualization, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, All authors reviewed, edited and approved the final manuscript. **Martin P. Bogsrud:** Conceptualization, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, All authors reviewed, edited and approved the final manuscript. **Trond P. Leren:** Conceptualization, Writing – review & editing, Writing – original draft, contributed to the conceptualization of the study, were responsible for data curation, All authors reviewed, edited and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2020.12.019>.

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