Current Causes of Death in Familial Hypercholesterolemia

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Research Article

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Abstract

Background: Familial hypercholesterolemia (FH) is a codominant autosomal disease characterized by high low-density lipoprotein cholesterol (LDLc) and high risk of premature cardiovascular disease (CVD). The molecular bases have been well defined and effective lipid-lowering is possible. This analysis aimed to study the current major causes of death of genetically defined heFH.

Methods: Case-control study designed to analyze life-long mortality in a group of heFH and control families. Data of first-degree family members of cases and controls (non-consanguineous cohabitants), including deceased relatives, were collected from a questionnaire and review of medical records. Mortality was compared among heFH, non-heFH, and non-consanguineous family members.

Results: We analyzed 813 family members, 26.4% of them, deceased. Among deceased, mean age of death was 69.3 years in heFH, 73.5 years in non-heFH, and 73.2 years in non-consanguineous, differences that were not statistically significant. Among them, CVD cause of death was 59.7% in heFH, 37.7.% in non-heFH, and 37.4% in non-consanguineous (*P*=0.012). These differences were greater restricting the analyses to parents' mortality. The hazard ratio of dying from CVD was 3.02 times higher (95% CI, 1.90-4.79) in heFH members in comparison with the other two groups (non-FH and non-consanguineous), who did not differ in their risk.

Conclusions: Current CVD mortality in heFH is lower and occurs later than that described in the last century but still higher than in non-FH. This better prognosis in CVD risk is not associated with changes in non-CVD mortality.

Introduction

Familial hypercholesterolemia (FH) is a codominant autosomal disorder and the most common monogenic metabolic disease in the population. The prevalence of heterozygous FH (heFH) is approximately 1/200-500 persons in most countries (1,2). FH is caused by mutations in the genes that control the cellular uptake of plasma cholesterol and that include the LDL receptor (*LDLR),* apolipoprotein B *(APOB),*pro-protein convertase subtilisin/kesin 9 *(PCSK9)* and *APOE* (1). HeFH patients show very high plasma concentration of low-density lipoprotein cholesterol (LDLc), approximately twice of non-FH subjects of the general population, often ranging between 250-400 mg/dL, deposits of cholesterol in superficial tissues such as corneal arcus and tendon xanthomas, and high risk of premature cardiovascular disease (CVD) in absence of adequate lipid-lowering treatment (3,4). The risk of developing premature CVD is increased 10 times in these patients with respect to the general population, especially coronary heart disease (CHD) in young patients (4,5). International heFH registries such as the British Simon Broome show an up to 100 higher risk of CHD in heFH men under 40 years of age with heFH in the pre-statin era, treatment that was not available until the late 1980s (6). The life expectancy of the heFH subjects had been calculated between 10-30 years lower for women and men, respectively, in relation to the non-FH population (7). In recent years, there has been a decrease in CVD in heFH, as we

have recently been able to verify in our environment (4,8) probably due to earlier diagnosis and intensive lipid-lowering treatment.

Two important facts have occurred in the morbidity and mortality analysis of the heFH in the last decades. First, the genetic bases of heFH have been studied in depth and the genetic study provides a certainty diagnosis that obviates the diagnostic bias based on CVD risk as one of the major criteria for heFH diagnosis (9); and, second current lipid-lowering drugs including statins, ezetimibe and PCSK9 inhibitors have substantially modified the lipid phenotype and consequently the clinical spectrum of the disease (5,10). In this way, if the treatment is well established during the first decades of life, heFH should be less aggressive disease than before. The complexity of the genetic FH background, the use of multiple drugs for decades, a larger life-expectancy associated with treatment and changes in environmental and social factors could lead to a much more heterogeneous phenotype than that described in the past century (5). In addition, other comorbidities could be associated to the heFH phenotype that were hidden by CVD, or associated to the lipid-lowering treatment, such as diabetes favored by statins (11). Knowing the effect of the different genetic types of heFH in the long term and the impact of prolonged lipid-lowering treatment are essential for an adequate management of this disease in the coming years.

The aim of this analysis was to study the current causes of cardiovascular and non-cardiovascular death of heFH and potential differences with a control population.

Patients And Methods

Aim, design, and participants

This is an observational, case-control study designed to describe current morbidity and mortality in heFH subjects. HeFH cases were recruited from the Lipid Unit at Hospital Universitario Miguel Servet, Zaragoza, Spain, and their non-consanguineous partners were recruited as controls. Data about first-degree family members of cases and controls, including deceased relatives, were collected from a participant questionnaire and review of their medical records. Written informed consent was obtained from each case and control included in the study; the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki; and the study protocol was previously approved by the Institution's ethics committee on research on humans (Comité Ético de Investigación Clínica de Aragón).

The inclusion criteria for cases consisted on the following requirements: age ≥ 30 and ≤ 60 years at the time of the enrollment in the study; genetically diagnosed heFH; and personal history of hypercholesterolemia with LDLc levels >220 mg/dL without lipid-lowering treatment. Controls were selected from non-consanguineous relatives of similar age (± 5 years) of heFH patients (partners of the case who cohabited with them); age ≥ 30 and ≤ 60 years at the time of inclusion in the study; and fulfilling that neither them nor any first degree relative had a clinical diagnosis of heHF and that they had LDLc <190 mg/dL without lipid-lowering drugs.

Clinical interview

Participants were interviewed to collect personal information about history of CVD disease, CV risk factors, comorbidities, medication use, lipid values, and hospitalizations, and besides, to perform a detailed family history including these data of all first-degree relatives (parents, siblings, and offspring), and age and cause of death of those deceased. Information about history of hypercholesterolemia, lipid-lowering drug use, and age and cause of death were confirmed from the patient's medical records. If a first-degree family members of a case presented LDLc >220 mg/dL in at least one occasion and/or LDLc >160 mg/dL while taking any statin they were tagged as belonging to the heFH group. The analysis groups were thus coined "heFH family members", "non-heFH family members", and "Control family members". In this report only data on family members deaths over the age of 18 years is presented.

Genetic study

All heFH cases interviewed in this study had a genetic diagnosis of heFH and were carriers of a "pathogenic" or "likely pathogenic" variant according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) (12) in *LDLR* (NM_000527.4), *APOB* (NM_000384.2) or *PCSK9* (NM_174936.3) genes. FH gene analysis were studied with the Progenika Biopharma Grifols (Derio, Spain) (13) or GEN inCode (Terrassa-Barcelona, Spain) (14) platforms.

Statistical Analyses

Data are expressed as mean standard deviation for numerical variables with normal distribution and were analyzed with the Student's t test, while those without normal distribution are expressed as median [interquartile range] and are analyzed with the Mann-Whitney U test. Qualitative variables are expressed as a percentage and were analyzed using the X2 test. For the comparison of non-dichotomous category variables, the ANOVA and Kruskal-Wallis tests were used. The mortality rates were calculated using the Kaplan-Meier estimate based on age, and the groups were compared using log rank test. The association between heFH and CV and non-CVD mortality was calculated using multivariate Cox's regression. A model was generated that included the covariate age, and it was calculated with techniques appropriate for analyzing complex samples to consider that data was clustered in families.

Results

Clinical characteristics of cases and controls

We recruited 166 subjects, 83 heFH cases and 83 controls. The mean ages were 54.3 years and 54.5 years, respectively, without differences in age and sex between the groups. BMI, systolic blood pressure and diastolic blood pressure were similar in both groups. Hypertension and diabetes (DM2) prevalence showed no differences either. CVD tended to be more prevalent in heFH cases than in controls 8.4% and 2.4% respectively (P=0.08). Untreated total and LDLc were higher in cases than in controls. Statin treatment was present in all cases and in 22.9% controls. The onset of the lipid-lowering treatment was 32.8 years in the heFH and 51.3 years in controls (Table 1).

Family study

We analyzed 813 first-degree family members of cases and controls within families of cases 211 members were heFH and 219 non-heFH. We discarded 11 first-degree family members of cases with an ambiguous heFH phenotype (Figure 1). The control family group was composed by 372 subjects.

CVD and non -CVD mortality among first-degree family members of cases and control

We identified 62 dead relatives in heFH family members, 53 in non-heFH and 100 in controls (Figure 1). The percentage of dead subjects and the mean age of the death were similar in the three groups, being slightly higher in the heFH family members, 29.4% compared with 24.2% in the non-heFH family members and 26.9 % in the control family members. Average death age was approximately 4 years less in the heFH group. The proportion of deaths due to CVD was higher among the heFH group (59.7% in heFH vs 37.7% in non-heFH and 37.4% in controls, *P*=0.012). Other causes of death, including cancer death, did not shown significant differences among the three groups (Table 2). Additionally, we studied mortality differences between men and women. The percentage of deceased subjects did not show differences between the groups, however, HeFH subjects died approximately 4 years earlier than non-heFH and controls, although the difference was not statistically significant. Death cause in men was CVD in 69% of heFH deceased versus 38.5% of non-heFH and 37.0% of controls respectively (P=0.01). The same pattern was observed in women although the age of death was about 7 years later in women than in men similarly in the 3 groups. (Table 3 and Table 4). The hazard ratio of dying of CVD in heFH was 2.85 times higher (95% CI, 1.73-4.69) in heFH with respect to the control family group, and without differences between non-FH and controls. This hazard ratio was 2.95 in men (95% CI, 1.52-5.75) and 3.44 in females in heFH (95% CI, 1.66-7.10) (Table 5). The separation of the curves appeared at the age of 50, to continue increasing progressively with age (Figure 2). This higher risk appeared approximately 5 years earlier in heFH men than in heFH women (Supplemental Figure 1).

CV or non - CVD mortality among parental family members of cases and controls.

Since most of the deaths corresponded to the parents of cases and controls, we analyzed mortality in this group of subjects. There were 116 deaths among fathers: 24 (72.7%) heFH, 35 (72.9%) non-heFH and 57 (70.4%) controls; and 77 deaths among mothers: 33 (66.0%) heFH, 13 (39.4%) non-heFH and 31 (37.8%) controls. The percentage of deaths from CVD was higher in heFH than in the other two groups, although the difference was significant only in men, and the age of death from CVD was younger in both men and women for heFH subjects. We did not find statistically significant differences in the non-CVD death (Figure 3), but the control family mothers had a trend to higher cancer death compared to heFH mother family (*P*=0.092) (Supplemental Tables 1 and 2).

Discussion

In the present work, we analyze the potential differences in mortality in a group of heFH families from a Lipid Unit comparing heFH, non-heFH, and non-consanguineous family members with the aim of update

CVD and non-CVD death in heFH in the era of lipid-lowering treatment. HeFH is a singular model to study the effect on mortality of hypercholesterolemia due to an increase in LDLc levels and their relationship with CVD events (15). In addition, heFH are usually under intensive lipid-lowering chronic treatment and our results are in line with the CVD benefit observed with the LDLc lowering in the general population (16,17). We hypothesized that the prevalence of CVD death has decreased during the last years in these patients and our results seem to support the case because CVD mortality in this group of families is lower and appeared later than heFH cohorts reported in the last decades of last century (7,17). However, we still find an increase in CVD death with respect to non-heFH, especially in the heFH men, who died 6.8 years younger compared to the other family groups. Traditionally, it has been considered that in heFH without lipid -lowering treatment, approximately 50% of men and 30 % of women will develop CVD before 50 years (18,19) with the life expectancy estimated to be 20 to 30 years lower (7). However, the CVD death could have been biased in those studies: Historically, heFH has been diagnosed clinically based on LDLc elevations, premature personal and familial CVD, and presence of tendon xanthomas or arcus cornealis. The most common criteria for diagnosis including those of the Dutch Lipid Clinic Network (20) and Simon Broome registry (21) include CVD o risk factors for CVD such as tendon xanthomas (18,22,23). In this way, the heFH subjects or their families in whom CHD prevailed, had more chances to get the clinical diagnosis of FH. The genetic characterization of FH in recent years have demonstrated that the heFH phenotype is more heterogeneous than previous belief including the presence of CVD. In a recent publication from The Netherlands, CHD was present in 7.4% of 25,137 genetically diagnosed heFH, in spite of the mean age was 38 and 71.1% were not on lipid-lowering drugs (24). Consequently, a significant proportion of heFH may have gone unnoticed while applying traditional diagnostic criteria.

Our cohort is based on very high LDLc levels (>220 mg/dl without lipid-lowering therapy) and a positive genetic test for a causative mutation in a canonical gene for FH. Furthermore, patients were referred to the clinic by their general practitioners because high LDLc (25). So, we think that our cohort has overcome previous bias. Robust evidence, including heFH observational studies, has demonstrated a reduction in major CVD events in patients who are taking lipid-lowering treatment when initiated early in life and maintained for years (26,27). Accordingly, the survival without CHD, with an early onset of statins in these subjects, could be quite similar to the rest of the population (28). In our study, we showed a large group heFH who were taking lipid-lowering treatment above 25 years on average. Furthermore, the majority of their heFH family members have been taking statins at some point in their lives. In addition, the prevalence of CVD estimated in this study, 7% in heFH, are in line with other studies in genetically defined heFH (24,29).

We have also analyzed non-CVD mortality in these genetically defined heFH families with a large history of lipid lowering drugs consumption with two purposes: First, to check whether lipid-lowering therapy could play a role in other comorbidities, and second, to explore whether the FH causing mutation itself might be associated to other morbidities other than CVD once heFH subjects live long enough without CVD, something that, until now, would have been hidden in the early mortality. In this study, non-CVD mortality did not show significant differences between heFH and non-FH in either sex group. There was a

tendency in the heFH females to die later from non-CVD causes than non-FH, even though the difference did not reach statically significance. We hypothesized that it could be due to healthier lifestyles in heFH subject such as our group showed previously (8).

Our study has some limitations. Its retrospective design only heFH who lived enough time are selected, so heFH subjects who died before the analysis, cannot be studied. The number of subjects studied, imposed by the difficulty to find large series of patients, allows us to identify differences in mortality in the large disease groups, if some rare disease is associated with the mutation or the treatment, this could have gone unnoticed. Finally, we have information about the time of treatment onset, but only in cases and controls could be completely corroborated. The strengths of our article include that all heFH cases have been genetically confirmed and that HeFH diagnosis was independent of CVD.

Conclusion

Our results show that current CVD mortality in heFH is lower and occurs later than that described in the last century but still higher than in non-FH. Probably, this is due to better control of the risk of CVD risk factors, especially prolonged lipid-lowering treatment. This better prognosis in CVD risk is not associated with changes in non-CVD mortality.

Abbreviations

BMI: body mass index

CHD: coronary heart disease

CVD: cardiovascular disease

DM: diabetes mellitus

FH: familial hypercholesterolemia

heFH: heterozygous familial hypercholesterolemia

HDLc: high-density lipoprotein cholesterol

LDLc: low-density lipoprotein cholesterol

LDLR: low-density lipoprotein receptor gene

Lp(a): lipoprotein(a)

PCSK9: pro-protein convertase subtilisin/kesin 9

Declarations

Ethics approval and consent to participate:

The study protocol has been previously approved by the Institution's ethics committee on research on humans (Comité Ético de Investigación Clínica de Aragón). C.I. P18/262

Consent for publication: “Not applicable” for that section

Availability of data and materials: Data available upon reasoned request.

Competing interests: The authors declare no conflict of interest

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Author contribution statement

Conceptualization, VM-B and FC; Data Curation VM-B, AMB, EJ, AC, FC. Formal Analysis VM-B, ML, and FC; Funding Acquisition, FC; Investigation, VM-B, AC, ML, and FC; Methodology, VM-B, ML, and FC; Project Administration, FC; Resources, FC; Software ML; Writing - Original Draft Preparation: VM-B, FC; Review: all authors.

All authors have read and approved the final manuscript.

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Tables

Table 1. Clinical and biochemical characteristics of heFH and control probands.

	heFH Cases	Controls	*P*
N	83	83	
Age (years)	54.3 (10.7)	54.5 (10.5)	0.884
Women, N (%)	45 (54.2)	44 (53.0)	0.876
Current smokers, N (%)	11 (13.3)	22 (26.5)	0.098
BMI (Kg/m^2)	25.8 (3.94)	26.3 (4.17)	0.479
Systolic blood pressure (mmHg)	123.1 (12.7)	123.3 (14.0)	0.956
Diastolic blood pressure (mmHg)	74.6 (8.97)	75.3 (9.97)	0.628
Hypertension, N (%)	24 (28.9)	16 (19.8)	0.172
Type 2 diabetes mellitus, N (%)	7 (8.4)	7 (8.4)	1.000
Cardiovascular disease, N (%)	7 (8.4)	2 (2.4)	0.087
Total cholesterol (mg/dL)	363 (412-306)	220 (198-252)	<0.001
LDL cholesterol (mg/dL)	283 (222-339)	130 (105-154)	<0.001
HDL cholesterol (mg/dL)	56.2 (13.4)	62.0 (24.2)	0.079
Triglycerides (mg/dL)	114 (52.3)	141 (154)	0.209
Glucose (mg/dL)	89.5 (18.8)	91.3 (20.1)	0.626
Statin treatment, N (%)	83 (100)	19 (22.9)	<0.001
Onset age of statin treatment (years)	32.8 (9.43)	51.3 (8.84)	<0.001

BMI denotes body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Data are summarized as mean (SD) or N (percentage).

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Table 2. Mortality among heFH and control first-degree family members

Data are summarized as mean (SD) or N (percentage). Test for raw differences using Chi^2 test.

Table 3. Mortality among heFH and control first-degree male family members

Data are summarized as mean (SD) or N (percentage). Test for raw differences using Chi^2 test.

	heFH family members	Non-heFH family members	Control family members	*P*
N	211	219	372	
Total death, N (%)	62 (29.4)	53 (24.2)	100 (26.9)	0.479
Age of death (years)	69.3 (13.9)	73.5 (16.2)	73.2 (13.8)	0.179
Age of Cardiovascular disease death (years)	65.9 (13)	77.5 (12)	77.5 (13.2)	0.001
Age of Non-cardiovascular death (years)	73.9 (13.8)	71.4 (17.6)	71.72 (14.6)	0.792
Cardiovascular disease death, N (%)	37 (59.7)	20 (37.7)	37 (37.4)	0.012
Non-cardiovascular death, N (%)	25 (40.3)	33 (62.3)	62 (62.6)	
Cancer death, N (%)	12 (48.0)	14 (42.0)	31 (50.0)	0.779
Other death, N (%)	13 (52.0)	19 (57.5)	31 (50.0)	
Statin treatment, N (%)	107 (50.7)	29 (13.2)	53 (14,2)	0.001

Table 4. Mortality among heFH and control first-degree female family members

Data are summarized as mean (SD) or N (percentage). Test for raw differences using Chi^2 test.

Table 5. Prospective multivariable Cox Regression Analysis of Predictive Factors for a cardiovascular death in the families group

	heFH family members	Non-heFH family members	Control family members	*P*
N	100	115	187	
Total death, N (%)	29 (29.0)	39 (34.2)	65 (34.8)	0.599
Age of death (years)	65.8 (13.0)	72.2 (16.1)	70.7 (14.4)	0.099
Age of Cardiovascular disease death (years)	62.2 (11.5)	78.7 (13)	71.2 (11.6)	0.001
Age of Non-cardiovascular death (years)	73.7 (13)	68.0 (17)	70.4 (15.8)	0.650
Cardiovascular disease death, N (%)	20 (69.0)	15 (38.5)	24 (37.0)	0.010
Non- cardiovascular death, N (%)	9 (31)	24 (61.5)	41 (63.1)	
Cancer death, N (%)	6 (66.7)	12 (50)	19 (46.3)	0.543
Other death, N (%)	3 (33.3)	12 (50.0)	22 (53.6)	

heFH family members	CVD death HR (95% CI)	CVD death HR (95% CI) *
All	3.02 (1.90-4.79)	2.85 (1.73-4.69)
Males	2.90 (1.59-5.29)	2.95 (1.52- 5.71)
Females	3.20 (1.55-6.63)	3.44 (1.66-7.10)
Non-FH family members	HR (95%CI)	HR (95%CI) *
All	0.81 (0.46-1.42)	0.98 (0.58-1.65)
Males	0.79 (0.49-1.57)	0.80 (0.41-1.53)
Females	0.95 (0.33-2.67)	1.02 (0.38-2.71)

95% CI, 95% confidence interval; HR, hazard ratio. HR (95%CI) *: confidence interval estimations calculate taking into account family clusters.

Figures

	heFH family members	Non-heFH family members	Control family members	*P*
N	111	104	185	
Total death, N (%)	33 (29.7)	14 (13.5)	34 (18.4)	0.010
Age of death (years)	72.4 (14.1)	77.2 (16.6)	78.1 (11.5)	0.178
Age of Cardiovascular disease death (years)	70.2 (13.5)	74 (15.0)	82.6 (8.7)	0.032
Age of Non-cardiovascular death (years)	74.1 (14.6)	80.3 (17.6)	74.3 (11.7)	0.513
Cardiovascular disease, N (%)	17 (51.5)	5 (35.7)	13 (38.2)	0.451
Non- cardiovascular death, N (%)	16 (48.5)	9 (64.3)	21 (61.8)	
Cancer death, N (%)	6 (37.5)	2 (22.2)	12 (57.1)	0.175
Other death, N (%)	10 (62.5)	7 (77.7)	9 (42.8)	

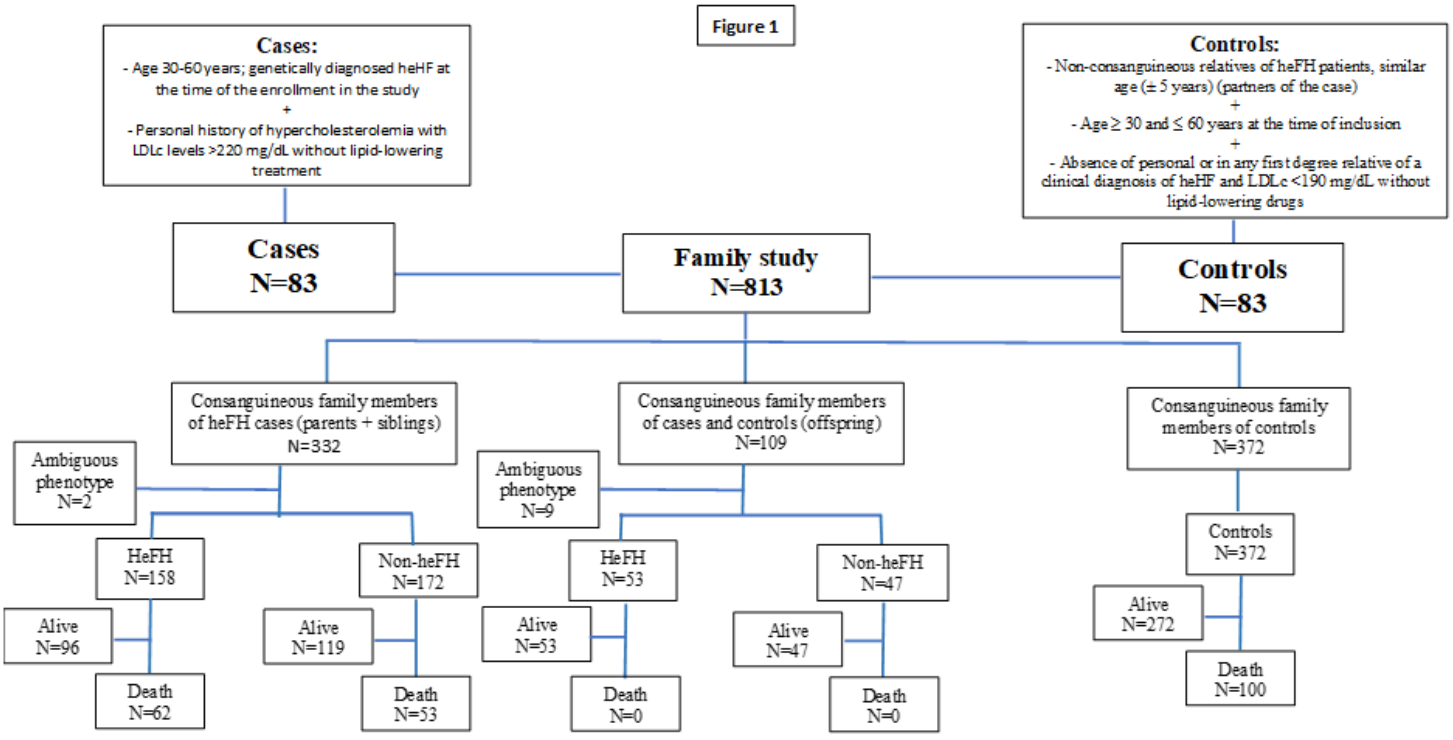
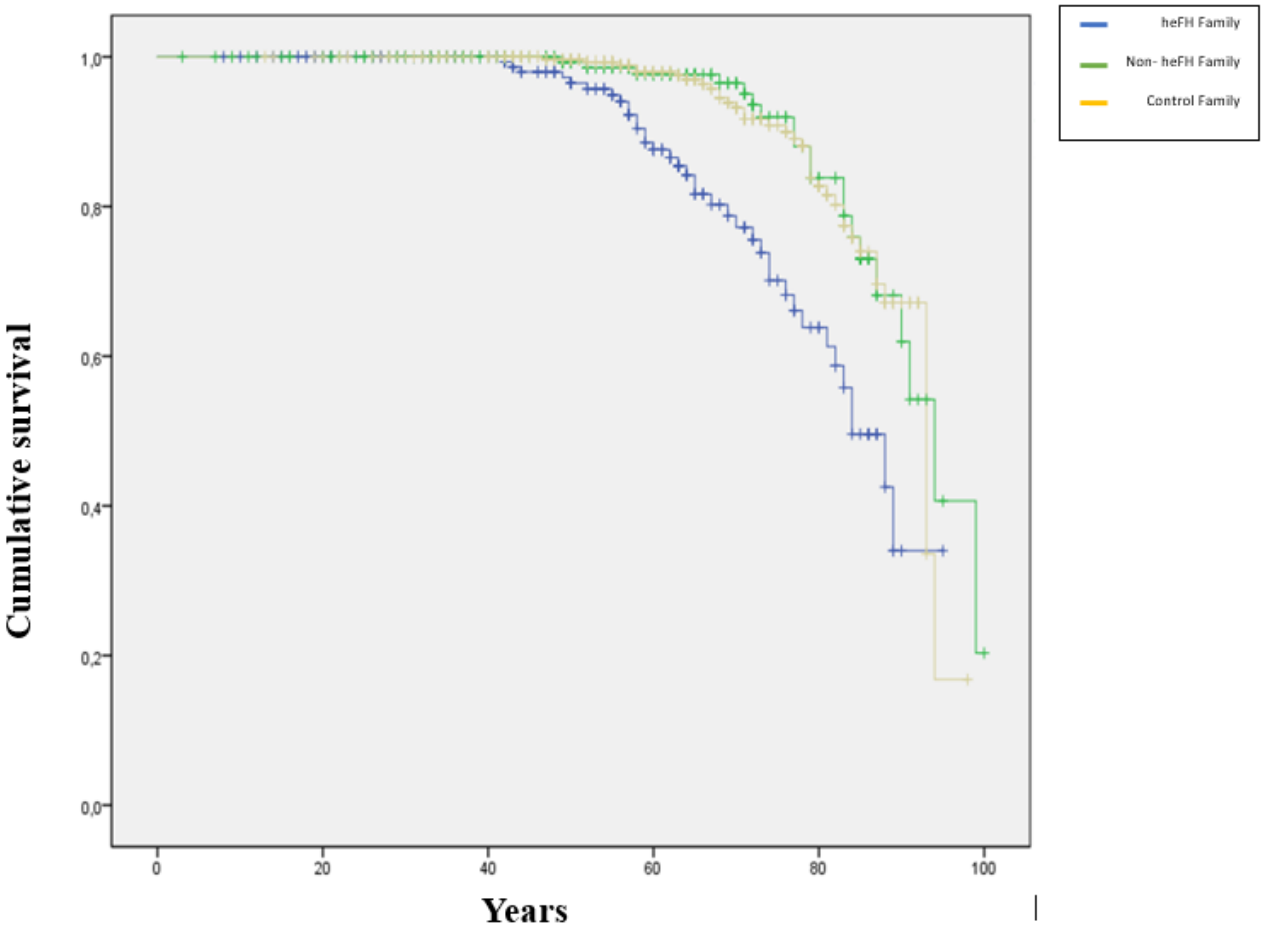


Figure 1

Study Flowchart

Figure 2.



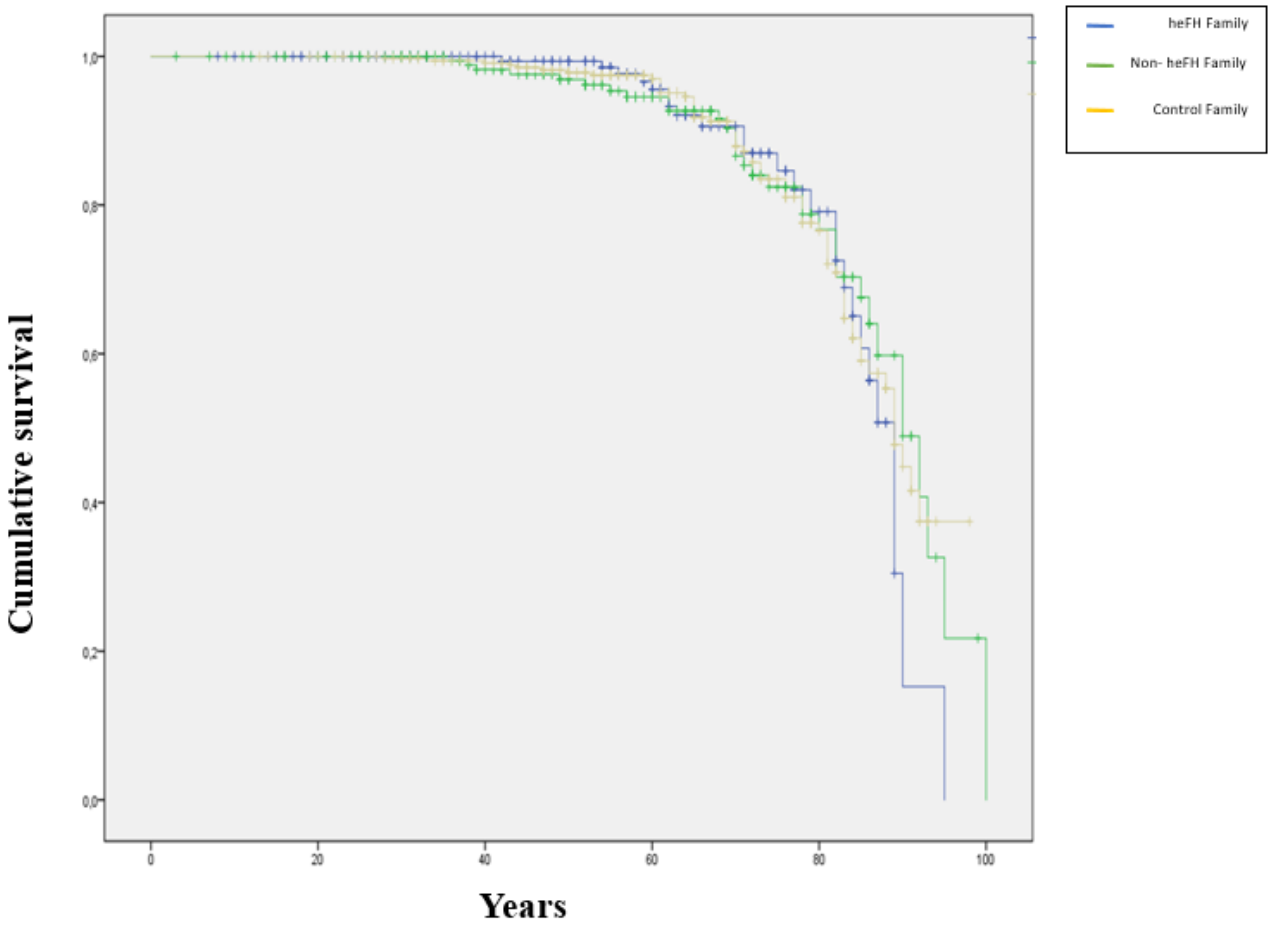
	20	40	50	60	70	80	90	100
heFH family members, N=207	194	154	125	87	50	25	1	0
N° cumulate death	0	0	5	15	23	30	37	37
Non-heFH family members, N =215	206	158	133	104	68	36	8	0
N° cumulate death	0	0	1	3	4	11	17	20
Control family members, N=355	351	325	279	202	125	68	14	0
N° cumulate death	0	0	1	5	13	24	33	37

Survival analysis free of cardiovascular death among groups.

Figure 2

Kaplan-Meier cumulative survival curves for cardiovascular death

Figure 3.



	20	40	50	60	70	80	90	100
heFH family members, N=207	194	154	125	87	50	25	1	0
N° cumulate death	0	0	1	5	9	14	24	25
Non-heFH family members, N =215	206	158	133	104	68	36	29	0
N° cumulate death	0	3	5	8	15	21	8	33
Control family members, N=355	351	325	279	202	125	68	14	0
N° cumulate death	0	3	7	9	25	39	59	61

Survival analysis free of non-cardiovascular death among groups

Figure 3

Kaplan-Meier cumulative survival curves for non-cardiovascular death

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementalfigure1pdf.pdf
- SupplementalTable.pdf