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Title

Factors predicting statin initiation during childhood in familial hypercholesterolemia:
importance of genetic diagnosis.

Short title

Predictors of statin treatment in children with HeFH

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Abstract

Objective To identify childhood and parental factors associated with statin initiation in children with heterozygous familial hypercholesterolemia (HeFH), including underlying genetic diagnosis or parental premature atherosclerotic cardiovascular disease (ASCVD)

Study design We conducted a multicenter cohort study including 245 HeFH child-parent pairs (National register REFERCHOL; 2014 to 2020). Demographic and clinical characteristics at the last visit were collected. Vascular disease in parents was defined as a history of ASCVD, and/or a coronary artery calcium score above 100, and/or at least one carotid stenosis (>50%). Statistical analysis included descriptive analysis, logistic regression for univariate and multivariate effects of statins, and a sensitivity analysis combining the characteristics of children and parents.

Results Only 135 (58%) of children, age 14 ± 3 years old, were treated with a statin. In multivariable analysis, the predictive childhood factors associated with statin treatment were: genetic diagnosis (OR=2.5, 95% CI [1.3; 4.9], $p=0.01$), older age (OR=4.4, 95% CI [1.8;10.6], $p=0.01$), more than 2 visits (OR 2.36 [1.18-4.73], $p=0.015$), and longer follow-up duration (OR=1.3, 95% CI [1.1;1.6], $p<0.001$). The predictive parental factor associated with childhood treatment was the presence of vascular disease (OR=2.4, 95% CI [1.0;5.7], $p=0.04$).

Conclusions HeFH confirmed with DNA-testing during childhood and a history of vascular disease in parents were independently associated with statin treatment in children with HeFH. Genetic diagnosis may be useful for cardiovascular prevention in children.

Heterozygous familial hypercholesterolemia (HeFH) is a common autosomal dominant disease affecting about 1 in 310 persons worldwide (1) (2). A high plasma concentration of low-density lipoprotein cholesterol (LDL-C) represents a major risk factor for atherosclerotic cardiovascular disease (ASCVD). Patients with HeFH have a dramatically increased risk of ASCVD after 20 years of age: 50% of untreated male patients have been shown to develop ASCVD before the age of 50 (3).

The follow-up of children with HeFH treated with statins by the age of 10 supports the potential benefit during adulthood regarding the risk of ASCVD (4) (5). The short-term benefits of initiating statin therapy during childhood are well established: improvement of lipid profile and endothelial function, and attenuation of the progression of atherosclerosis (6) (7). Long-term benefits have been demonstrated recently, too, with a reduction in the cumulative incidence of cardiovascular events and death from cardiovascular causes at 39 years among patients treated during childhood compared with their affected parents not treated during childhood (4). It appears that statin initiation in childhood may lead to a prognosis, which is similar to that of non-HeFH patients. International guidelines recommend the initiation of statins as first-intention treatment at 8-10 years of age in children with HeFH, with an LDL-C target < 130 mg/dL or a 50% LDL-C reduction from baseline level (5) (8). There is a compelling need to identify and treat HeFH early during childhood in order to maximize the therapeutic benefits (5).

Regardless, parents and physicians may be reluctant to treat children. Less than half of children with HeFH are treated (9) (10) (11). Few data exist on the reasons why children with HeFH are not treated according to these guidelines. Depending on their specialty (general practice versus lipid clinics, for example), physicians may have different views about the relevance and urgency to start statins or to implement genetic testing (14).

Our primary objective was to determine those predictive factors for initiation of statins. We hypothesized that a definitive genetic diagnosis or cardiovascular familial history could promote statin treatment in children.

Methods

This is a multicenter national, registry-based (REFERCHOL), retrospective and prospective cohort study. The national French registry of FH (REFERCHOL) was established in 2015 by the Nouvelle Société Francophone d'Athérosclérose (NSFA) as previously described (15). The cohort was registered with the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM, the French agency for medicine safety) and received an ID-RCB declarant number: 2014-A01549-38. For the present study, participants were prospectively enrolled between December 2014 and December 2020, and retrospective data from 1981 to 2020 were also collected. All adult patients, such as children with HeFH, signed an informed consent.

Because international recommendations are to treat children with statins starting at the age of 8, we included patients with HeFH from 8 to 18 years old and their parents with HeFH, both of whom were followed in the registry REFERCHOL. HeFH diagnosis was genetic or clinical for children and parents. In the absence of genotyping data, the clinical diagnosis of HeFH was defined for parents by a Dutch Lipid Clinic Network (DLCN) value ≥ 8 , indicating a definite HeFH diagnosis, and for children by either a LDL-C value >130 mg/dL and parents with a genetic mutation, or by an LDL-C value >160 mg/dL and parents with a DLCN value ≥ 8 (5). We excluded children harboring genetic mutations other than HeFH, those who were less than 8 years old at their last visit (treatment with a statin possible from the age of 8 years), those who had a first-degree relative other than a parent (brother or sister) with hypercholesterolemia, and those whose parental data were missing.

The process of a “classical” pediatric consultation in the lipid clinic includes the presence of at least of one parent with the child, if possible the parent suffering from FH; if a brother or sister less than 18 years old also has FH, then they may also attend the same consultation. If the parent or child refuses a statin despite discussion, a proposal is made to discuss such further during the follow-up consultation. If the statin treatment is accepted, then a regular follow-up twice a year is organized. Most of the time, children were seen until the age of 18 at the same clinic.

Demographic and clinical characteristics were collected at the last visit to the lipid clinic. For children, age was classified in 3 categories: ≥ 8 and < 10 years, ≥ 10 and < 14 years, and ≥ 14 and < 18 years. For genotyped patients, DNA was isolated and the genetic diagnosis of HeFH was evaluated at enrollment. Assessment of laboratory values, including a serum lipid profile, was performed in the clinical laboratory attached to each lipid clinic, using assay methods subjected to quality control. LDL-C max corresponded to the highest level of LDL-C recorded during the follow-up (i.e. baseline LDL-C without treatment).

Statin treatment included all statin drugs. The statin regimen was defined in 3 classes (low, moderate, and high) according to the dosage and the intensity of effects, as defined by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines (16). Loss to follow-up and missing data were quantified and compared with the cohort to evaluate bias.

ASCVD included coronary heart disease (acute coronary syndromes, myocardial infarction and unstable angina, percutaneous coronary intervention, or coronary artery bypass graft), stroke or transient ischemic attack, peripheral artery disease (defined as carotid endarterectomy, carotid angioplasty, peripheral artery revascularization, or surgical bypass), resuscitated sudden death, and cardiovascular death (17). A family history of early CV events was defined by the occurrence of the first event before 55 years of age in men and before 65

years of age in women among first-degree relatives. Family history was limited to the first-degree relatives of the parents (their own parents or their siblings), meaning the second-degree relatives of the children. The duration of follow-up was defined as the time from the enrollment visit to the last available visit at the lipid clinic.

Vascular disease was defined as follows: i) a coronary calcium (CAC) score > 100 in parents, and/or ii) at least one carotid stenosis ($>50\%$) in parents, and/or iii) a history of a cardiovascular event in the family (parents or their first-degree relatives). CAC score and data on carotid explorations were available only for the parents. Tissue within the vessel wall with a CT number of 130 Hounsfield units (HU) or more was defined as calcified, and the amount of calcium was typically classified using the so-called “Agatston score,” which considers the area and the peak density of calcified lesions.

Statistical analysis

Data were expressed as count (percentage) for categorical variables and as mean \pm standard deviation (SD) for continuous variables. The characteristics of children with or without treatment were compared using the students t test or the Wilcoxon rank-sum test for continuous variables, and the chi-square or Fishers exact test for categorical variables. P values <0.05 were considered as statistically significant. Comparison of the characteristics of parent(s) whose child(ren) was (were) either treated or not treated were evaluated similarly. Univariate and multivariate effects of statin treatment in children were analyzed using a logistic regression and expressed as odds ratios (OR) and the corresponding 95% confidence intervals (CI). Multivariable analyses used a stepwise approach with a statistically significant threshold of 0.05 for covariates entry. A sensitivity analysis combining the characteristics of both children and parents was conducted. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). We adhered to the STROBE checklist.

Results

Among the 623 pediatric patients from the registry, 245 (39.4%) child-parent pairs were included (Figure 1). The vast majority of exclusions (87%) were related to missing parental data or children with a first-degree relative other than a parent. The characteristics of excluded patients (378, 60.6%) were compared with those of our cohort: excluded children were younger (13.00 (3.71) vs 13.86 (3.02) years, $p=0.01$) with a slightly lower LDL cholesterol maximum (2.4 (0.79) vs 2.55 (0.58) g/L, $p=0.02$), but the age at initiation and frequency of statin treatment were similar between the 2 groups of patients.

Among all included children, 125 (53%) were girls without difference in the sex ratio between the two groups (statin treatment, no statin treatment). At last visit, 122 (52%) children were adolescents (i.e. ≥ 14 years and < 18 years), and the follow-up duration was 2 ± 2 years. There were 135 (58%) children in the statin group (Table I). Statin-treated children were significantly older than untreated children (age: 14 ± 3 vs 13 ± 3 years, $p=0.01$). A minority (15, 11%) of treated children received combination therapy (statin+ ezetimibe) (data not shown). Among the untreated children at the last visit, two-thirds had only one visit ($n=66$, 67%), and one-third returned but almost all children were not treated after the second visit ($n=30$, 91%). A total of 166 (71%) children had a genetic diagnosis at the age of 10 ± 4 years, and 147/166 (88%) harbored a mutation of the LDL receptor (LDLR) gene. The proportion of patients with a genetic diagnosis was higher among statin-treated children (81% vs 58%, $p=0.0001$; Table I). Interestingly, the age of statin treatment initiation was similar between genetic- and clinical-diagnosed children, ie 10 ± 3 years. The pretreatment total cholesterol (TC) levels were 22% higher and the LDL-C levels were 23.7% higher in statin-treated children compared with non-treated children ($p < 0.0001$ for both comparisons). At last visit, statin-treated children had a 24.7% lower LDL-C level than untreated children ($p < 0.0001$). During the follow-up, the LDL-C level of children treated with statins decreased

on average by 116 mg/dL (-43%; Table I). The percentage of children reaching the LDL target recommended at the last visit are 12% and 37% for non-treated and treated children respectively.

Parents were classified depending on whether their child received statin treatment or not. Among the 198 parents with HeFH, there was no difference in the sex ratio (100 mothers, 51%; $p = 0.46$), nor in the parents' age ($p = 0.54$) at the last visit between the two groups (Table II). The diagnosis was performed by genotyping for 159 (80%) parents at an age of 43 ± 10 years. The vast majority of parents was treated (174, 88%) without a difference between the two groups of parents. Parents initiated statin treatment at an average age of 30 ± 12 years.

Interestingly, there was no significant difference regarding the prevalence of cardiovascular risk factors (smoking, diabetes, and hypertension) nor in lipid-lowering therapy use between the two parent groups. In addition, the total cholesterol and LDL-C concentrations at last visit were similar between the two groups of parents (Table II).

More than a quarter of parents ($n=55$, 28%) had a personal history of ASCVD, without a difference between the two groups of parents (Figure 3; available at www.jpeds.com). The age of the parents at first ASCVD event was 43 ± 11 years and was similar between the two groups. However, familial history of cardiovascular events was more frequent among the parents of a treated child (52/86, 62%) (Figure 3). Half of parents had a coronary atherosclerosis evaluation with a coronary artery calcium score (102/198, 51%). The mean CAC score was 234 ± 526 , without a significant difference between the two groups. However, parents of statin-treated children were more likely to have a CAC score > 100 (22/47, 47% vs 14/55, 25%, $p=0.02$; Figure 3). Vascular disease was found more frequently among parents with a statin-treated child than among parents with a non-treated child (43/86, 50% vs 40/112,

36%, $p=0.04$). Results were similar when considering the parents plus their first-degree relatives together.

The predictive childhood factors significantly associated with being a statin-treated child were in univariate analysis: genetic vs clinical diagnosis, older age, to have more than one visit, higher maximal total cholesterol and LDL-C concentrations at diagnosis and at last visit, and longer follow-up duration (Figure 2A and Table III; available at www.jpeds.com). In multivariable analysis, the predictive childhood factors significantly associated with being a statin-treated child were: 1) genetic vs clinical diagnosis (OR=2.5, 95% CI [1.3; 4.9], $p=0.004$), 2) older age (being aged 10 to 14 years rather than 8 to 10 years: OR=4.4, 95% CI [1.8; 10.6], $p=0.001$), 3) having more than one visit (OR 2.36 [1.18-4.73], $p=0.015$), and 4) longer follow-up duration (OR=1.3, 95% CI [1.1; 1.6], $p<0.001$) (Figure 4; available at www.jpeds.com; and Table III).

The parental predictive factors associated with having a child treated with a statin rather than untreated were in univariate analysis: 1) parental genetic vs clinical diagnosis, 2) longer follow-up duration, 3) presence of a premature ASCVD event and 4) a younger age of the first ASCVD event in the first-degree relatives, 5) parental CAC score above 100, and 6) the presence of vascular disease in the parents or in the family (Figure 3 and Table IV; available at www.jpeds.com). In multivariable analysis, the significant predictive parental factor remained the presence of a familial vascular disease (OR=2.4, 95% CI [1.0; 5.7], $p=0.046$) among family members (Figure 4).

Discussion

The identification of factors predicting treatment might help promote early initiation of statin treatment in children. Our results not only confirmed some of previously described factors influencing statin initiation, but also clarified specific points and identified new ones.

In the present study, HeFH confirmed in DNA-testing compared with a clinical diagnosis in children was an independent predictive factor of statin treatment during childhood. This result strengthens a recent Scandinavian study suggesting that the 3-5 times significantly higher prescription of statins for children in Norway, compared with Denmark or Sweden, may be due to the more widespread use of genetic testing in this country (19). Similarly, a previous European study has also reported that countries in which the percentage of children diagnosed with a HeFH mutation was the highest (the Netherlands and Greece), also had the highest percentage of children under statin treatment (20). Interestingly, in a prospective study, to promote molecular genetic testing as part of a cascade of genetic screening led to significantly more frequent statin treatment, and to a significant improvement in the lipid profile (21). These results are only associations and not causal relationships; however, they suggest that implementing routine genetic testing in clinical practice might increase the proportion of children treated with statins.

We showed that statin-treated children had a longer follow-up in the lipid clinic than the untreated children. Genetic testing may take several months to be realized. We can hypothesize that the parents and/or the physicians wait for the formal genetic diagnosis to initiate statin therapy in children.

In registry studies, the time to begin treatment during follow-up is a critical point because patients are often untreated at the first referral visit, and many of those may have had only one visit. Indeed, in our cohort, the majority of untreated children went only to the first visit. Several hypotheses are possible to explain this high frequency of untreated patients after the first visit: 1) many patients who did not want treatment did not return for follow-up in the lipid clinic; 2) some patients might have gotten a prescription at the next visit, if older, or if they had higher LDL-C levels; 3) they were waiting for the results of the genetic analysis, which may argue for a positive impact of definitive diagnosis related to genetics. However, in

the untreated group with a single visit, the mean delay between the visit and the collection of the data was more than twice as long compared with the mean delay between the first and the second visit in children with at least 2 visits (34.02 (21.30) vs 14.33 (9.11) months). These results suggest that patients with a single visit appear to be a subset of patients who did not return to the lipid clinic, either because they wished to wait for treatment or did not wish to be treated/consulted.

In the present study, older age was associated with a higher rate of statin initiation. Similarly, in a European study, the proportion of children treated with statins has been found higher in older age groups: children over 10 were about twice more likely to be treated with a statin compared with children under 10 at last follow-up (9) (20). Concerns about very long-term consequences of statins in younger children may explain the reluctance to treat younger children; a specific questionnaire-based survey could confirm this hypothesis.

We also found that higher LDL levels in children were significantly associated with more frequent statin treatment in children. A high LDL-C level is a classic criterion to treat children with HeFH (18), and may induce more concern from parents as well as physicians, leading to treating the child more frequently.

In our study, family history of vascular disease was predictive of statin treatment in children. A personal history of early ASCVD has previously been associated with higher statin use in adults (24). Similarly, in a large UK registry, the reasons for not being on lipid-lowering medication included the weak or absent evidence of familial history of early ASCVD (9). The parents' views on treatment in children have been analyzed in a qualitative study using in-depth interviews (13): the majority of parents with familial or personal experience of cardiovascular disease had a strong sense of illness vulnerability, and wanted to protect their children from such problems (22) (23) (12) (13). Therefore, it seems reasonable to suppose that the concern raised by a cardiovascular event itself, or by abnormalities

indicating a possible future cardiovascular incident (positive imagery and arterial stenosis), would increase parents' sensibility and therefore promote treatment in children.

There are some limitations to the interpretation of our results. First, more than half of the children from the registry were excluded from this study. This was mainly because the parent affected by HeFH had no medical follow-up in the same center and no longer participated in the registry. To evaluate this bias, we compared the excluded patients to our cohort: the percentage of children treated, the statin regimen, and the mean age at the initiation of treatment were not statically different. Second, this is a national study and the data may not apply to other countries, where screening methods or current healthcare systems differ. Third, the main limitation of such a study based on a registry is selection bias: only patients evaluated in specialized centers were included. Previous studies have demonstrated that medical care of HeFH differs according to the healthcare setting patients attend (general practice or lipid clinics, for example) (22). Fourth, among the untreated children at the last visit, two-thirds had only one visit, which may limit the interpretation of the results because we cannot exclude that they just did not return independently of other risk factors (genetic results for example).

In conclusion, undertreatment of children with HeFH remains a problem, with just over half of children treated despite being followed up in specialist lipid clinics. In addition, the mean LDL-C levels remains higher than the recommended therapeutic target in the majority of treated patients. Prospective studies are necessary to evaluate if genetic testing in children and non-invasive testing of consenting parents for ASCVD would really encourage early statin treatment in children, as suggested by our results.

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Figure 1:

This flowchart indicates that among the 623 selected children, 378 were excluded mainly because parent's data were missing (followed up in another center). Among the 245 included children, 166 children had a genetic diagnosis.

Figure 2:

This figure indicates the predictive factors to treat children with statins with statistical significance and Odd Ratio in univariate analysis for children's predictive factors (Figure 2-A) and parent's predictive factors (Figure 2-B).

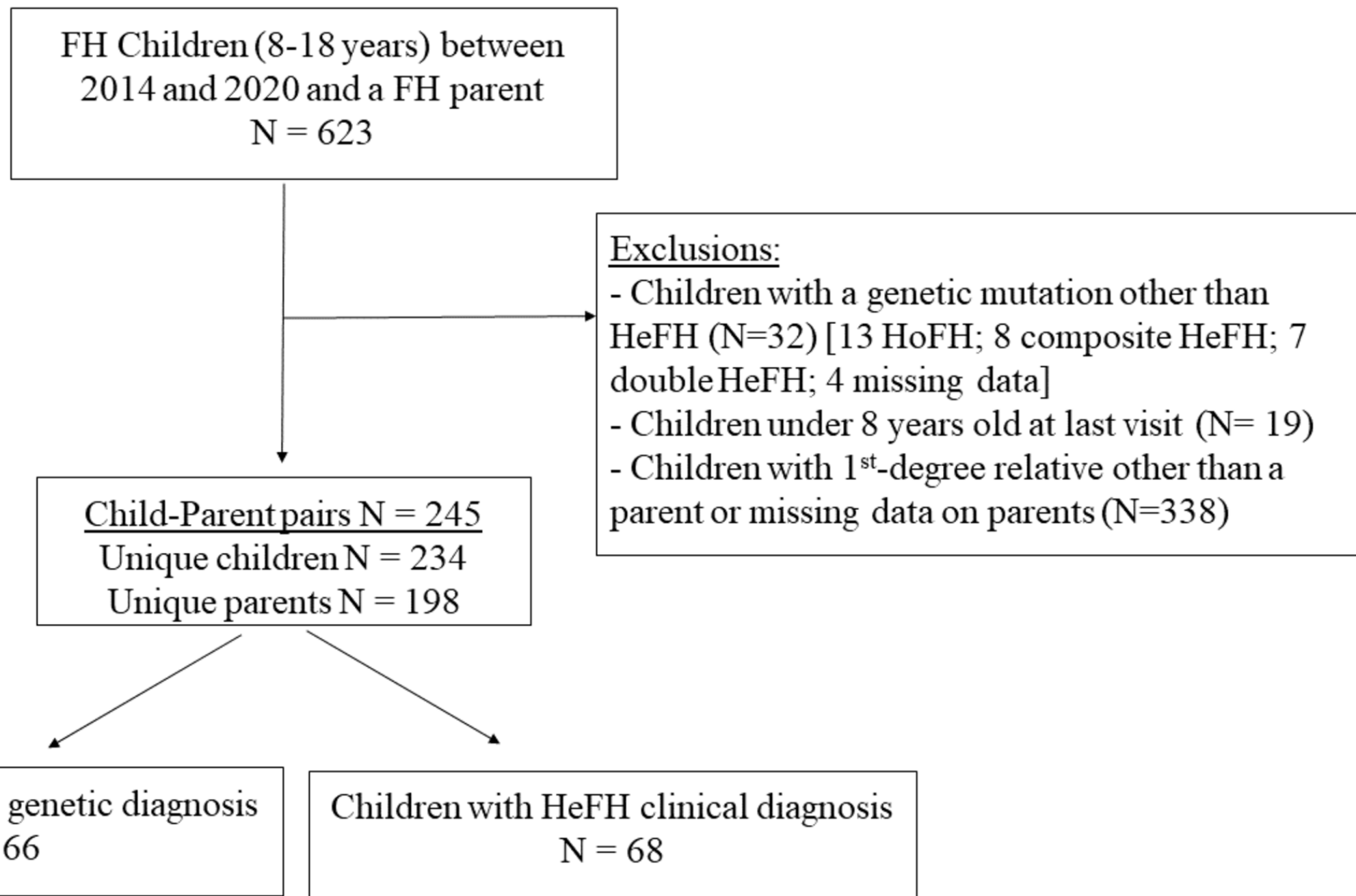
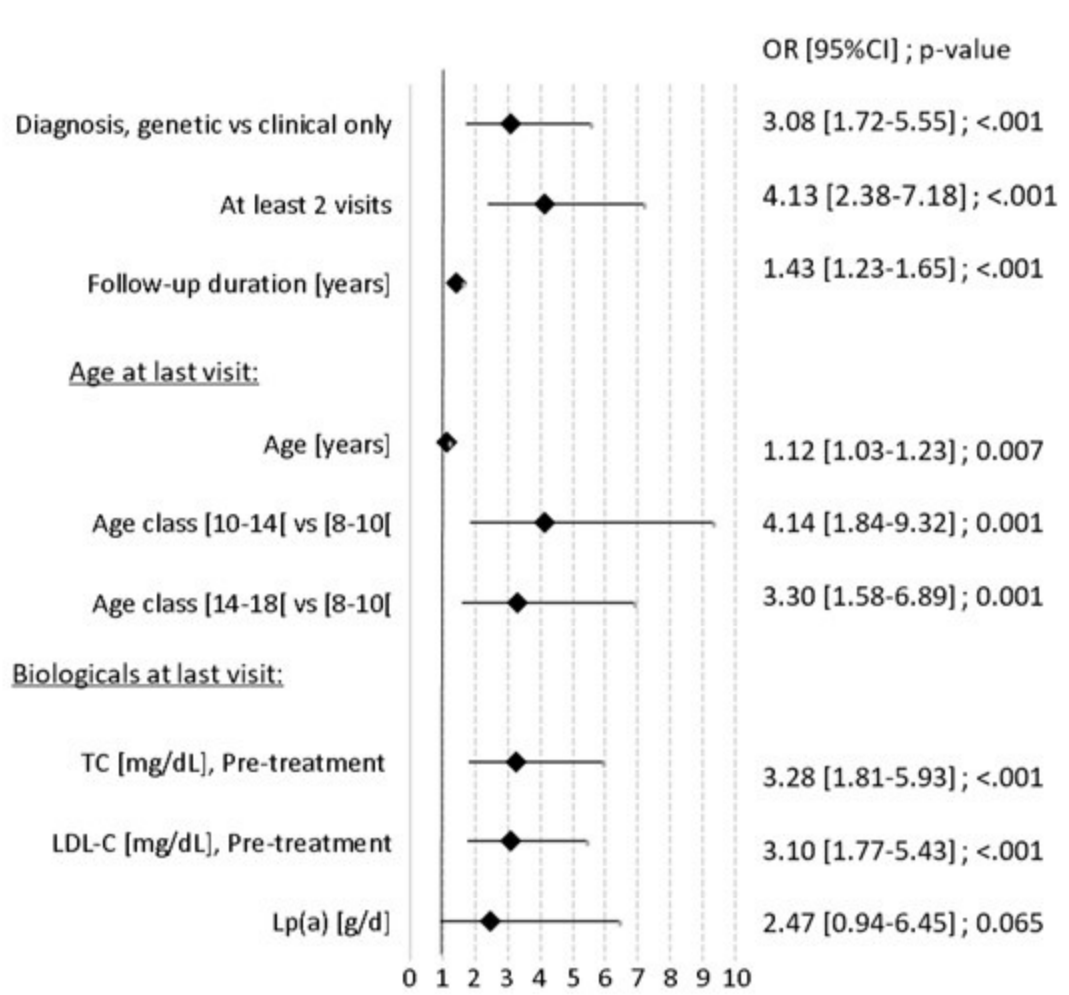


Figure 1: Flowchart

A) Child characteristics



B) Parents characteristics

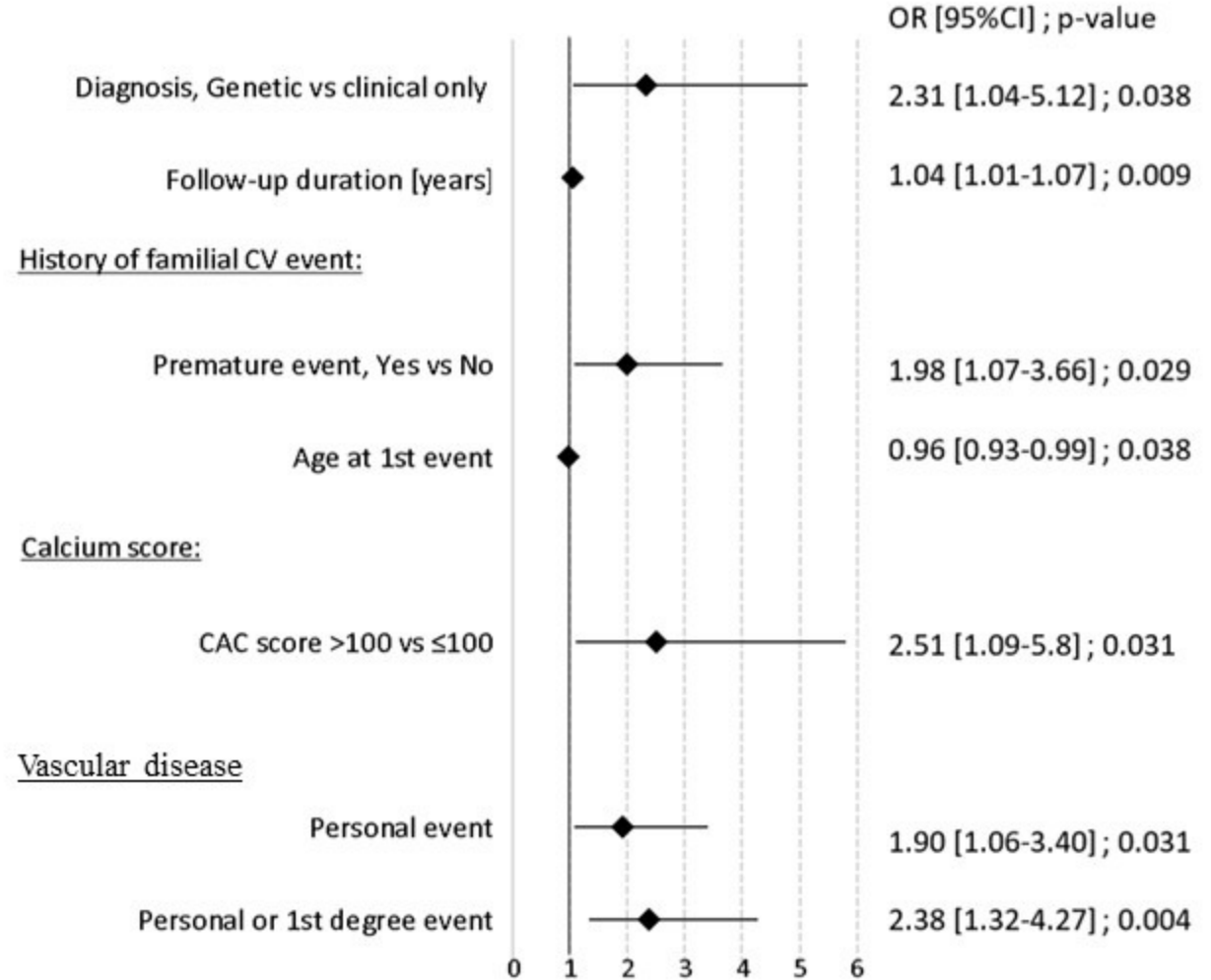
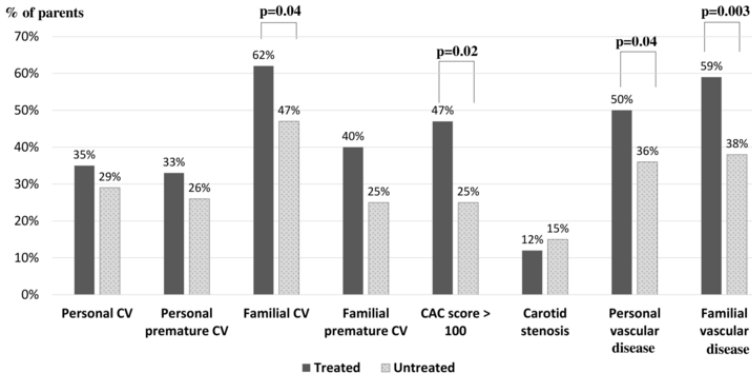


Figure 2 Univariate analysis of predictive factors for FH children being treated with statins



Supplementary Figure 3: Distribution of cardiovascular status in the parents and family of children treated or untreated.

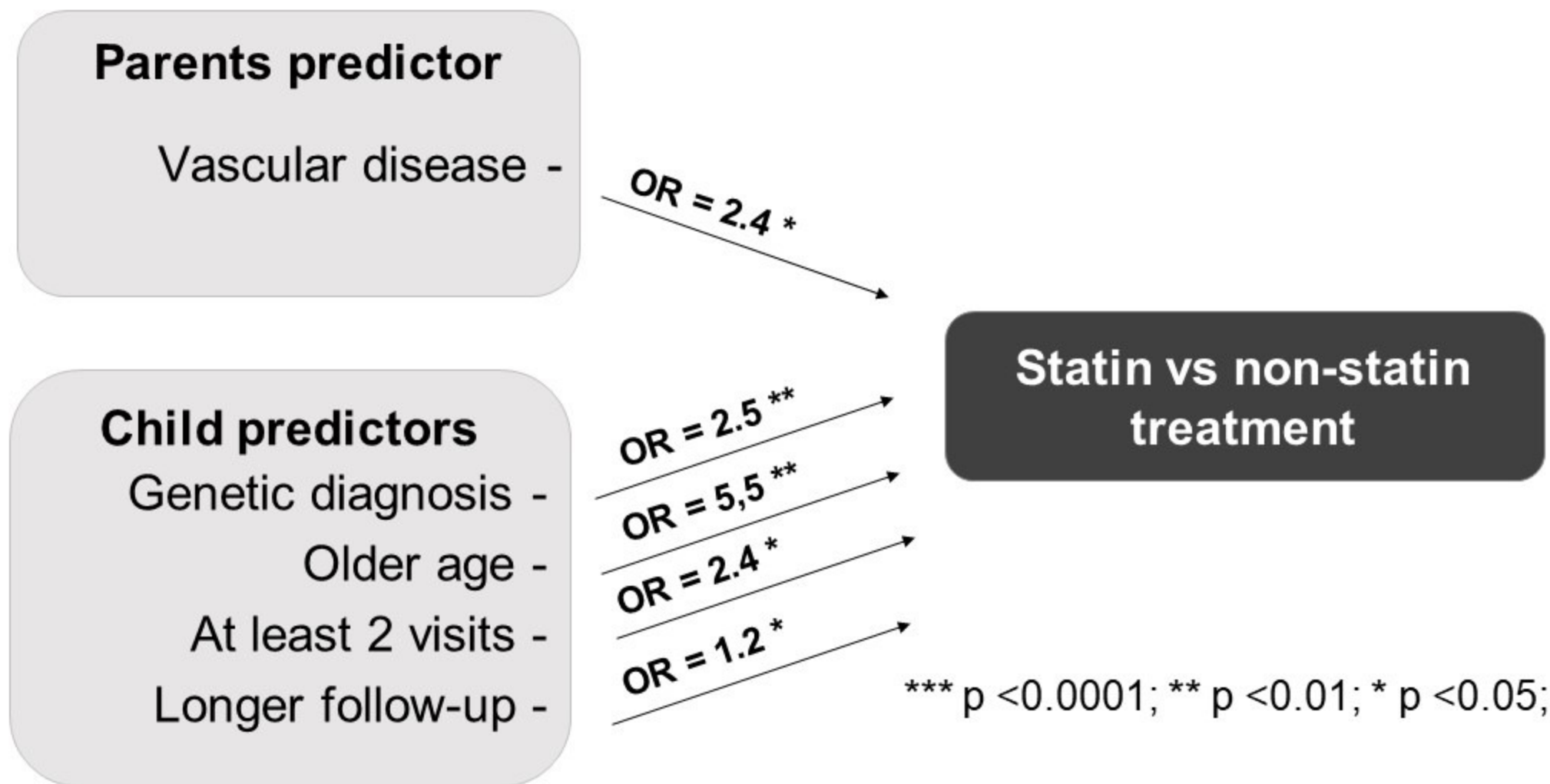


Figure 4 Multivariate analysis of predictive factors for FH children being treated with statins

Table 1. Characteristics of children at last visit.

Characteristics	Last visit			p-value
	Untreated children (N=99)	Statin-treated children (N=135)	Total (N=234)	
Female (n, %)	54 (55%)	71 (53%)	125 (53%)	p = 0.77
Age [years] (mean±SD)	13±3	14±3	14±3	p = 0.01
Anthropometry				
Height [cm] (mean±SD)	154±18	161±13	158±15	p = 0.01
Weight [kg] (mean±SD)	46±16	52±13	50±14	p = 0.01
Type of diagnosis (n, %)				
Clinical only	42 (42%)	26 (19%)	68 (29%)	p = 0.0001
Genetic	57 (58%)	109 (81%)	166 (71%)	
Age at diagnosis [years]				
genetic diagnosis (mean±SD)	11±5	9±4	10±4	p = 0.02
clinical diagnosis (mean±SD)	12±3	14±3	13±3	p = 0.04
Gene mutation (n, %)				
<i>LDLR</i>	46 (81%)	101 (92%)	147 (88%)	p = 0.11
<i>APOB</i>	10 (18%)	7 (6%)	17 (10%)	
<i>PCSK9</i>	1 (2%)	1 (1%)	2 (1%)	
Heredity of mutation (n, %)				
Both parents	1 (1%)	0 (0%)	1 (1%)	p = 0.49
Mother	41 (53%)	51 (49%)	92 (51%)	
Father	36 (46%)	53 (51%)	89 (49%)	
TC [mg/dL] (mean±SD)	271±58	217±39	240±55	p < 0.0001
Pre-treatment [mg/dL] (mean±SD)	308±52	344±62	330±61	p < 0.0001
LDL-C [mg/dL]				
Pre-treatment (mean±SD)	235±50	268±59	255±58	p < 0.0001
Last visit [mg/dL] (mean±SD)	202±56	152±37	173±52	p < 0.0001
Age at initiation of statin treatment [years] (mean±SD)	NA	10±3	10±3	
Lp(a) [mg/d] (mean±SD)	0.35 (0.44)	0.58 (0.58)	0.45 (0.52)	p=0.06
Follow-up duration [years] (mean±SD)	1±2	3±2	2±2	p < 0.0001

Abbreviations: *ApoB*, apolipoprotein B gene; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein cholesterol Receptor gene; *MLPA LDL*, Multiplex ligation-dependent probe amplification of LDLR; *PCSK9*, Proprotein Convertase Subtilisin/Kexin Type 9 gene; SD, standard deviation; TC, total cholesterol

Table 2 Characteristics of parents at last visit.

Characteristics	Untreated child(ren) (N=112)	Statin-treated child(ren) (N=86)	Total (N=198)	P-value
Female (n, %)	54 (48%)	46 (53%)	100 (51%)	p = 0.46
Age [years] (mean±SD)	48±9	49±8	49±9	p = 0.54
Age class (n, %)				
<30 years	1 (1%)	2 (2%)	3 (2%)	p = 0.78
≥30 and ≤59 years	100 (89%)	76 (88%)	176 (89%)	
≥60 years	11 (10%)	8 (9%)	19 (10%)	
CV risk factors				
Hypertension (n, %)	15 (14%)	16 (20%)	31 (17%)	p = 0.30
Type 2 diabetes (n, %)	5 (5%)	5 (6%)	10 (6%)	p = 0.86
Smoking status (n, %)				
Smoking	46 (43%)	35 (44%)	81 (44%)	p = 0.86
No smoking	61 (57%)	44 (56%)	105 (56%)	
Type of diagnosis (n, %)				
Clinical only	27 (24%)	12 (14%)	39 (20%)	p = 0.07
Genetic	85 (76%)	74 (86%)	159 (80%)	
Gene mutation (n, %)				
<i>LDLR</i>	77 (90%)	66 (90%)	143 (90%)	p=0.40
<i>APOB</i>	7 (8%)	3 (4%)	10 (6%)	
<i>PCSK9</i>	2 (2%)	4 (6%)	6 (12%)	
Heredity (n, %)				
Both parents	6 (11%)	4 (10%)	10 (10%)	p = 0.91
Mother	21 (38%)	17 (43%)	38 (40%)	
Father	29 (52%)	19 (48%)	48 (50%)	
TC [mg/dL]				
Pre-treatment (mean±SD)	393±104	403±113	398±108	p = 0.56
last visit (mean±SD)	225±95	211±65	219±83	p = 0.27
LDL-C [mg/dL]				
Pre-treatment (mean±SD)	300±99	309±107	304±102	p = 0.57
last visit (mean±SD)	153±91	145±66	150±81	p = 0.48
Lp(a) mg/L (mean±SD)	0.51 (0.58)	0.42 (0.38)	0.47 (0.50)	p=0.74
Treatment				
Treatment at last visit (n, %)	97 (88%)	77 (89%)	174 (88%)	p = 0.53
Age at initiation of statin treatment (mean±SD)	31±13	29±11	30±12	p = 0.59
Statins (n, %)	94 (84%)	72 (84%)	166 (84%)	p = 0.97
Follow-up duration [years] (mean±SD)	6±8	10±10	8±9	p = 0.01
History of CV events				
Personal CV events				
Age at 1 st CV (mean±SD)	45±13	40±9	43±11	p = 0.10
Familial CV events				
Age of 1 st CV event (n, %)	50 (15)	44 (13)	47 (14)	p = 0.06

* Vascular disease = History of CV event and/or CAC > 100 and/or presence of carotid stenosis

Abbreviations: *ApoB*, apolipoprotein B gene; CAC score, coronary artery calcium score; HU, Hounsfield Unit; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein cholesterol Receptor gene; *MLPA LDL*, Multiplex ligation-dependent probe amplification of LDLR; *PCSK9*, Proprotein Convertase Subtilisin/Kexin Type 9 gene; SD, standard deviation; TC, total cholesterol

Supplementary Table 3. Univariate and multivariate analyses of predictive childhood factors of statin treatment in children

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender, F vs M	0.9	[0.5; 1.5]	0.767	-		
Age [years]	1.1	[1.0; 1.2]	0.007	-		
Age class [10; 14[vs [8; 10[4.1	[1.8; 9.3]	0.001	5.5	[1.8; 10.9]	0.001
[14; 18[vs [8; 10[3.3	[1.5; 6.8]	0.001	2.2	[0.9; 5.1]	0.051
Diagnosis, genetic vs clinical only	3.0	[1.7; 5.5]	< 0.001	2.5	[1.3; 4.8]	0.008
TC						
Pre-treatment	3.2	[1.8; 5.9]	< 0.001	-		
LDL-C [mg/dL]						
Pre-treatment	3.1	[1.7; 5.4]	< 0.001	-		
Lp(a)	2.4	[0.9; 6.4]	0.065	-		
At least 2 visits, Yes vs No	4.1	[2.4; 7.2]	<0.001	2.4	[1.2; 4.7]	0.015
Follow-up duration [years]	1.4	[1.2; 1.6]	< 0.001	1.2	[1.0; 1.5]	0.050

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol, Lp(a), lipoprotein a; OR, odds ratio; TC, total cholesterol.

Supplementary Table 4. Univariate and multivariate analyses of parental predictive factors of statin treatment in children

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender, F vs M	1.2	[0.6; 2.1]	0.505			
Age [years]	1.0	[0.9; 1.0]	0.449			
class ≥ 60 vs [30; 59]	1.0	[0.3; 2.7]	0.929			
Diagnosis, Genetic vs clinical only	2.3	[1.0; 5.1]	0.038			
Treatment, Yes vs No	1.6	[0.6; 4.2]	0.325			
Age at initiation of statins	0.9	[0.9; 1.0]	0.686			
Statins, Yes vs No	1.5	[0.6; 3.7]	0.373			
TC [mg/dL]						
Pre-treatment [mg/dL]	1.0	[0.7; 1.4]	0.497			
Last visit	0.8	[0.5; 1.2]	0.460			
LDL-C [mg/dL]						
Pre-treatment [mg/dL]	1.0	[0.7; 1.4]	0.639			
Last visit	0.8	[0.6; 1.2]	0.497			
Follow-up duration [years]	1.0	[1.0; 1.0]	0.009			
History of CV events						
Personal CV events						
CV event, Yes vs No	1.3	[0.6; 2.4]	0.412			
Premature CV event, Yes vs No	1.3	[0.7; 2.5]	0.366			
Age at 1st CV event	0.9	[0.9; 1.0]	0.118			
Number of CV events	1.2	[0.7; 2.3]	0.416			
Familial CV events						
CV event, Yes vs No	1.7	[0.9; 3.1]	0.0568			
Premature CV event, Yes vs No	1.9	[1.0; 3.6]	0.0288			
Age at 1 st CV event	0.9	[0.9; 0.9]	0.0377			
Number of CV events	1.3	[0.9; 1.9]	0.0754			
CAC score >100 vs ≤ 100	2.5	[1.0; 5.8]	0.031			
Carotid stenosis, yes vs no	1.3	[0.5; 3.1]	0.469			
Vascular disease*						
Personal	1.9	[1.0; 3.4]	0.031			
Personal or familial	2.3	[1.3; 4.2]	0.004	2.4	[1.0; 5.7]	0.0459

* Vascular disease = History of CV event, and/or CAC > 100, and/or presence of carotid stenosis

Abbreviations: CAC score, coronary artery calcium score; CI, confidence interval; CV, cardiovascular; F, female; LDL-C, low-density lipoprotein cholesterol; M, male; OR, odds ratio; TC, total cholesterol.