**Title: Classification, prevalence and cardiovascular risk of different types of hypercholesterolemia**

**Running title: Cardiovascular risk in hypercholesterolemia**

**Authors' names:** Fernando Civeira MD[a,b], Estibaliz Jarauta MD[a,b], Victoria Marco-Benedí PhD[a,b]. Ana M. Bea[a], Rocío Mateo-Gallego PhD[a,b], Itziar Lamiquiz-Moneo PhD[a,b], Irene Gracia-Rubio PhD[a,b], Daniel Bello-Alvarez[a], Martín Laclaustra MD[a,b], M.Teresa Tejedor PhD[b], Salvador Olmos PhD[b], Ana Cenarro PhD[a,c]

**Author' affiliations:**

[a]Hospital Universitario Miguel Servet, IIS Aragón, CIBERCV, Spain

[b]Universidad de Zaragoza, Zaragoza, Spain

[c]Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza, Spain

**Corresponding author:** Dr. Fernando Civeira. Hospital Universitario Miguel Servet. Avda Isabel La Catolica 1-3, 50009, Zaragoza, Spain
Email: civeira@unizar.es

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**Abstract**

Background. The frequency, clinical characteristics and atherosclerotic cardiovascular disease (ASCVD) risk of the different types of hypercholesterolemia is not well established. The objectives of this work were to identify the cause of hypercholesterolemia and whether such cause confers a different ASCVD prognosis.

Methods. The analysis included 3476 probands with primary hypercholesterolemia, of whom 3283 (94.8%) were followed a mean of 9.33±5.8 years for ASCVD. Genetic analysis of canonical familial hypercholesterolemia (FH) genes, polygenic risk score for hypercholesterolemia and lipid concentrations including lipoprotein(a) (Lp(a) ) were used to classified hypercholesterolemia.

Results. The diagnoses were: heterozygous FH (HeFH), n=400 (11.5%); hyperlipoproteinemia(a) (HyperLpa), n=181 (5.2%); polygenic hypercholesterolemia, n=434 (12.5%); hyperLpa+polygenic hypercholesterolemia, n=128 (3.7%); multifactorial, n=1562 (45.0%); and idiopathic, n=769 (22.1%). At baseline, LDL cholesterol was higher in HeFH, and ASCVD prevalence higher in HyperLpa. Other clinical and biochemical characteristics did not differ among hypercholesterolemia subgroups. HyperLpa subjects showed a lower survival rate than the other hypercholesterolemia groups (p=0.001). The variables independently associated with ASCVD events during the follow-up were age, male sex, the presence of ASCVD, diabetes or hypertension at baseline, current smokers and Lp(a) and HDLc concentrations, the latter inversely associated with ASCVD events. Total mortality was independent of the type of hypercholesterolemia.

Conclusion. Genetic hypercholesterolemia has a worse prognosis for ASCVD than non-genetic hypercholesterolemia. Among them, those with elevated Lp(a) have the worst

prognosis. Conventional lipid-lowering treatment for LDLc appears to be less effective in hypercholesterolemia due to HyperLpa than in other hypercholesterolemias.

**Keywords:** primary hypercholesterolemia, classification, familial hypercholesterolemia, mortality

## Introduction

The increase in the blood concentration of cholesterol transported in low-density lipoproteins (LDLc) is an independent factor for the development of cardiovascular diseases due to atherosclerosis (ASCVD) (1). LDLc reduction has been shown to be very effective in reducing ACVD events, which is why important scientific societies (2-4) and health systems (5) recommend LDLc reduction in people at high ASCVD risk or very high LDLc concentrations.

High LDLc concentrations are usually considered ≥190 mg/dL (6,7), and pharmacological treatment is usually indicated in adults if significant reductions are not achieved with lipid-lowering diet and life style modifications (2-5). Many subjects with LDLc concentrations ≥190 mg/dL have a primary form of hypercholesterolemia; around 2% are due to the monogenic form called Familial Hypercholesterolemia (FH) (8), and more often a polygenic contribution (9) or very high concentrations of lipoprotein(a) (Lp(a)) (10,11) are responsible. In a substantial high percentage (>50%) (12), the cause of the increase in LDLc is unknown, and it has been proposed to call this type of hypercholesterolemia "idiopathic primary hypercholesterolemia" (13).

Despite the heterogeneity in the etiology of primary hypercholesterolemia, lipid-lowering treatment recommendations do not take into consideration the etiology of hypercholesterolemia (2). However, the etiological basis of hypercholesterolemia plays an important role in the prognosis of patients and, at least subjects with mutations in *LDLR*, the gene that encodes the LDL receptor and the main cause of FH, had a higher risk of CV disease than other hypercholesterolemias with similar levels of LDLc (8,14).

The objectives of this work are to identify the cause of hypercholesterolemia and to identify whether such cause confers a different ASCVD prognosis.

## Material and Methods

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Subjects

This is an observational study, in which all consecutive unrelated subjects aged ≥14 years who were studied at the Lipid Unit of the Hospital Universitario Miguel Servet, Zaragoza, Spain, from January 2000 to December 2024 with the clinical diagnosis of hypercholesterolemia (LDLc ≥ 130 mg/dL or non-high-density lipoprotein cholesterol (non-HDLc) ≥ 160 mg/dL) without the use of lipid-lowering drugs, and following a lipid-lowering diet were included in this study (n=4109). After excluding secondary causes, including the presence of renal disease with glomerular filtration rate <30 mL/min and/or macroalbuminuria (n=30, 0.6%), cholestasis (direct bilirubin >1 mg/dL, n=47, 1.1%), hypothyroidism (thyroid-stimulating hormone >6 mIU/L, n=86, 2.1%), pregnancy (n=0), autoimmune diseases (n=6, 0.1%), or treatment with protease inhibitors, high doses of steroids, retinoids or cyclophosphamide treatment (n=7, 0.2%) (10), a total of 3933 subjects, 2053 (52.2%) men and 1880 (47.8%) women were included in a protocol for the etiological diagnosis of their hypercholesterolemia.

Lipid Analysis

Lipid and lipoprotein analyses were performed on EDTA plasma samples collected after at least a 10-hour overnight fast, following a lipid-lowering diet, and without lipid-lowering drugs for at least 4 weeks in the absence of cardiovascular disease or very high risk. In subjects under lipid-lowering drug therapy, total cholesterol (TC) and triglycerides (TG) concentrations were estimated by multiplying by 1.43 corresponding to a mean reduction of 30% in patients receiving statins or fibrates, respectively (15). TC and TG levels were determined by standard enzymatic methods. HDLc was measured directly by an enzymatic reaction using cholesterol oxidase (UniCel DxC 800;

Beckman Coulter, Inc, Brea, CA). LDLc was calculated using Friedewald's formula if TG <400 mg/dL. Apolipoprotein (apo) B and Lp(a) were determined by IMMAGE kinetic nephelometry (Beckman-Coulter, Inc) (16).

Protocol for the diagnosis

The protocol for the diagnosis of the different types of primary hypercholesterolemia is represented in Figure 1 and derived from reference 13. After exclusion of secondary causes (n=176), homozygous *APOE2/E2* (n=25), and subjects with TG > 400 mg/dL (n=432), the diagnosis of primary hypercholesterolemia was considered in presence of LDLc ≥ 130 mg/dL or non-HDLc ≥ 160 mg/dL with a diagnostic genetic study or strong family history, or in presence of very high values of LDLc or non-HDLc (≥ 190 mg/dL and 220 mg/dL, respectively) (n=2429).

Definitions

**Heterozygous (mono-allelic) familial hypercholesterolemia (HeFH):** Hypercholesterolemia being heterozygous for a rare variant identified in *LDLR, APOB* or *PSCK9* genes classified as "pathogenic" or "likely pathogenic," according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) (17) or the p.(Leu167del) variant in *APOE* (18).

**Hyperlipoproteinemia(a) (HyperLpa):** Presence of very high values of LDLc or non-HDLc (≥ 190 mg/dL and 220 mg/dL, respectively) with Lp(a) ≥100 mg/dL + adjusted for Lp(a) LDLc < 190 mg/dL and non-HDLc < 220 mg/dL and absence of HeFH.

**Polygenic hypercholesterolemia (PH)**: Presence of very high values of LDLc or non-HDLc (≥ 190 mg/dL and 220 mg/dL, respectively) with PRS >75th percentile of the distribution in our population and absence of HeFH.

**Idiopathic primary hypercholesterolemia (IPH):** Primary hypercholesterolemia in the absence of HeFH, hyperlipoproteinemia(a) and polygenic hypercholesterolemia

criteria and LDLc >190 mg/dL and/or non-HDLc >220 mg/dL and any predisposing secondary condition or promoting factor including type 2 diabetes, obesity (body mass index (BMI) ≥30 kg/m2) or high alcohol consumption (≥30 g/day in men and ≥20 g/day in women).

**Multifactorial hypercholesterolemia (MH)**: Hypercholesterolemia with LDLc ≥130 mg/dL or non-HDLc ≥160 mg/dL and absence of criteria for primary and secondary hypercholesterolemia.

Genetic Analysis

The presence of functional mutations in *LDLR* (NM_000527.4), *APOB* (NM_000384.2), and *PCSK9* (NM_174936.3) genes were determined using the Progenika Biopharma Grifols (Derio, Spain) (19) or GENinCode (Terrassa-Barcelona, Spain) (20) platforms in all subjects suspected of having monogenic hypercholesterolemia because of severe hypercholesterolemia with tendon xanthomas in the proband or first degree relative, or in the presence of LDLc ≥220 mg/dL if age <40 years or ≥230 mg/dL if age ≥40 years in the proband or in a first-degree relative plus dominant hypercholesterolemia pattern, with vertical transmission in multigenerational pedigrees and approximately 50% affected first degree relatives, with only one affected parent (13). These platforms include single nucleotide variations (SNVs), large rearrangements, and copy number variations. Monogenic hypercholesterolemia was considered in all subjects with severe primary hypercholesterolemia, vertical transmission of hypercholesterolemia in the family, and LDLc >95th percentile of the Spanish population in at least one first-degree relative. Additionally, a polygenic risk score (PRS) for hypercholesterolemia was calculated in subjects with primary hypercholesterolemia based on 12 common SNVs previously identified as LDLc-raising from genome-wide association consortium studies from European-Caucasian

populations (21). Genotyping to calculate the PRS was performed with the Genotype of Beadchip Infinium Global Screening Array-24 v3.0 and TOPMED imputation at the Spanish National Cancer Research Center (CNIO), Madrid, Spain.

All patients provided informed consent to a protocol previously approved by the Ethics Committee of our institution. The samples from patients at Hospital Universitario Miguel Servet were provided by the Biobank of the Aragon Health System (PT17/0015/0039), integrated into the Spanish National Biobanks Network, and were processed following standard operating procedures.

Follow-up

Since their inclusion in the study, all patients were reviewed once or twice per year in the unit until death. The treatment protocol was homogeneous, aiming for concentrations of LDLc and/or the concentration of non-HDLc in subjects with TG >200 mg/dL according to individual ASCVD risk. Treatment objectives were established according to the main international recommendations, considering the presence of risk factors in the subject. Cardiovascular morbidity and mortality were defined by the primary International Classification of Disease (ICD) -9 and ICD-10 and was defined as a composite of nonfatal ischemic stroke, nonfatal myocardial infarction, hospitalization for unstable angina, revascularization procedure and cardiovascular death. Survival status was analysed by reviewing the electronic medical records of the subjects, from which information on ASCVD and death was extracted. All subjects followed at least 1 year were included in the follow-up study.

Statistical Analysis

Analyses were performed using the statistical computing software IBM SPSS Statistics 21.0. Quantitative variables are expressed as mean ± standard deviation, except for variables not following a normal distribution, expressed as median (interquartile range).

The p-value was calculated by ANOVA test or Kruskal-Wallis H test as appropriate. Qualitative variables are expressed as a percentage and were analyzed by the chi-square test. ASCVD during the follow-up was calculated using Kaplan-Meier estimates, and the groups were compared by log-rank tests. The association between mortality and hypercholesterolemia groups was calculated using proportional hazards Cox regression. A multivariable Cox regression model was generated and included the covariables showed in Table 1. Afterwards, we fitted the new model keeping all the variables that showed $p < 0.2$ and major CVD factors including hypercholesterolemia groups.

**Results**

Subjects

The study included 3476 probands after ruling out secondary causes (n=176), subjects with *APOE2/2* genotype (n=25) and subjects with TG >400 mg/dL (n=432). 2429 (69.9%) were classified as having primary hypercholesterolemia, and 1504 (61.9%) met criteria for possible monogenic disease. The final diagnoses of the 3476 subjects were: HeFH, n=400 (11.5%); HyperLpa, n=181 (5.2%); polygenic hypercholesterolemia, n=434 (12.5%); hyperLpa+polygenic hypercholesterolemia, n=128 (3.7%); multifactorial, n=1562 (45.0%); and idiopathic, n=769 (22.1%) (Figure 1 and Table 1). At the start of follow-up in the Lipid Unit, the mean age was 50±13.6 years, with subjects with HeFH (45.3±14.9 years) being younger than the rest of the groups. Women predominated in all groups except in the multifactorial subgroup. Total cholesterol, LDLc, non-HDLc, and apoB concentrations were higher in subjects with HeFH. The lowest prevalence of diabetes was in subjects with HeFH, and the lowest prevalence of ASCVD was in the idiopathic subgroup. Except for Lp(a) concentrations, PRS value, and presence of diabetes, which were classification criteria, the rest of the

clinical and laboratory variables were similar between the idiopathic, polygenic and HyperLpa subgroups (Table 1).

Polygenic risk score for hypercholesterolemia (PRS)

The PRS value was normally distributed across the entire population. There was a positive association between the PRS value and LDLc concentration only in subjects with primary hypercholesterolemia excluding HeFH and subjects with HyperLpa (Supplementary Table 1). The difference between the first and last decile of PRS was 14 mg/dL (Supplementary Figure 1), and the differences were concentrated in the last quartile compared to the other quartiles (Supplementary Figure 2). In the regression analysis, the PRS was not associated with LDLc concentration in subjects with HeFH or HyperLpa. In contrast, PRS was an independent factor associated to LDLc (Supplementary Table 2)

Total mortality during follow-up

The mean follow-up was 9.33±5.8 years. 3283 probands (94.8% of the probands) were included in the follow-up. The reasons for exclusion were follow-up <1 year (n = 20, 0.6%) and loss to follow-up (n = 171, 4.9%). There were 168 deaths (5.1%), distributed as cancer 64 (38.1%), ASCVD 52 (31.0%), infectious 21 (12.5%), neurodegenerative 19 (11.3%), other 7 (4.2%) and unknown 5 (3.0%).

There were no significant differences in overall mortality when all subjects were analyzed by type of hypercholesterolemia or when only death before the age of 90 years were considered (Log Rank=0.362) (Supplementary Figure 3). Factors independently associated with mortality in the Cox regression analysis before the age of 90 included male sex, presence of ASCVD at baseline, current smoking at baseline, and HDLc concentrations, the latter negatively associated (Supplementary Table 3).

ASCVD during lifetime

Only the first ASCVD event was considered in this analysis and included events before and after the study in the Lipid Unit. There were 424 subjects with ASCVD events, 307 before the start of follow-up and 117 during follow-up. The vascular distribution was as follows: coronary 283 (66.7%), cerebro-vascular 78 (18.4%), peripheral or aortic 59 (13.9%), and mesenteric 4 (0.9%).

Variables negatively associated with a first ASCVD event were female sex and HDLc concentration, and positively associated variables were a family history of premature ASCVD, the presence of diabetes and hypertension, personal history of tobacco consumption, PRS and Lp(a) concentration (Table 2).

In the survival analysis by hypercholesterolemia group, there were significant differences in the ASCVD-free period, with shorter survival in subjects with HyperLpa and longer in idiopathic forms ($P<0.001$) (Figure 2, panel A); lower in genetic forms (HeFH, HyperLpa and polygenic) with respect to non-genetic forms (multifactorial and idiopathic ($p=0.001$) (Figure 2 panel B); lower in genetic forms versus idiopathic forms ($p<0.001$) (Figure 2 panel C); and considering only genetic forms, it was lower in forms with HyperLpa versus the rest ($p=0.002$) (Figure 2, panel D). The estimated differences in ASCVD event-free survival were approximately 14 years between subjects with HyperLpa with respect to idiopathic forms (Figure 2, panel A).

<u>ASCVD during follow-up</u>

Since the start of the study in the Lipid Unit there were 188 ASCVD events, 71 were recurrent events (23.1% of subjects with ASCVD at the beginning of the follow-up) and 117 first ASCDV events (3.7% of subjects without ASCVD at the beginning of the follow-up). The vascular distribution was as follows: coronary n=137 (65.2%), cerebro-vascular n=42 (20.0%), peripheral or aortic n=29 (13.8%), and mesenteric n=2 (1.0%).

In the survival analysis, only HyperLpa subjects showed a lower survival rate than the other hypercholesterolemia groups (p=0.001) (Figures 3 and 4). The variables independently associated with events during follow-up were age, male sex, the presence of ASCVD, diabetes, hypertension at baseline, current smokers and Lp(a) and HDLc concentrations, the latter inversely associated with ASCD events (Table 3).

## Discussion

In this work, we establish the frequency, clinical characteristics, and ASCVD risk of different types of hypercholesterolemia, classified according to the pathogenetic mechanism of their production. This study confirms that primary hypercholesterolemia has diverse etiological bases, and that only in slightly less than half of them can a genetic basis be demonstrated with current procedures. This study supports the idea of designation of those primary hypercholesterolemia without demonstrated genetic background as "idiopathic" until we can better understand their production mechanisms (13). It also confirms that in 7.5% of subjects with primary hypercholesterolemia, this can be explained by their elevated Lp(a) concentration, so the term "HyperLpa" seems very appropriate for this population (10,22).

Several additional results of this study are worth highlighting. Except for some subjects with HeFH, who have differential clinical stigmata and higher LDLc concentrations, the remaining clinical forms of hypercholesterolemia have almost identical clinical features (12). They are predominantly female, have similar mean LDLc, TG, and HDLc concentrations, as well as age, BMI, prevalence of diabetes or hypertension, and a family history of premature ASCVD. Thus, they can only be differentiated through genetic testing and Lp(a) concentrations. This clinical overlap of the different clinical forms also includes monogenic clinical forms, since, as previously observed (23,24). In

our study, only 27% of subjects with primary hypercholesterolemia and clinical suspicion of HeFH can demonstrate a pathogenic variant in the canonical FH genes. We cannot rule out the possibility that variants in other genes, yet to be discovered, may be the cause, or that genetic techniques may fail to detect some pathogenic variants, although this is unlikely because several genome-wide studies in these type of subjects fail to identify associated *loci* other than those already known (25), and very rare FH phenocopies such as sitosterolemia or lysosomal acid lipase deficiency (26) have been rule out in our genetic analysis. Therefore, it seems important at this time to perform a genetic study for the diagnosis of HeFH and to reserve this designation for those families in which a pathogenic variant is detected (13). Several factors have contributed to the overdiagnosis of HeFH, including phenotypic overlap between different lipid disorders (23,24), limited availability of genetic testing in certain settings (27), and the clinical imperative to diagnose a genetic condition that facilitates access to specific treatments (15). Something similar occurs with polygenic hypercholesterolemia, which should be reserved for those subjects in whom can be reliably demonstrated that they do not have HeFH and that their polygenic load is high. Our data shows that subjects above the 75% percentile of the PRS population distribution are those who have a higher LDLc and that there are no differences in LDLc in the highest three deciles of the PRS. While the characterization of the etiopathogenic basis is important for a better understanding of the disease and the development of new therapeutic strategies in the future, our study demonstrates that knowledge of the etiology has prognostic implications for present-day ASCVD. Our study confirms the data from the UK Biobank, showing that subjects with genetic forms of hypercholesterolemia of genetic origin have a higher risk than those in which this component cannot be demonstrated, and all of them are independent of LDLc concentration (12). This fact is striking and

possibly reflects that concentration at a given time in life is not a faithful reflection of LDLc burden throughout life. Unlike the UK Biobank cohort, in our cohort, subjects with HyperLpa have a worse ASCVD risk than other forms of hypercholesterolemia, including HeFH. The criteria used in the aforementioned study are any Lp(a) > 50 mg/dL, whereas our study uses higher concentrations and diagnostic criteria that are very different from the concept of HyperLpa. There are no prospective studies in our setting on the contribution of Lp(a) to ASCVD. The paradox of the lower impact of ASCVD risk factors in Mediterranean countries compared to other populations is well known (28), but this may not apply to Lp(a). Regardless of the comparative risk with respect to HeFH, our study clearly confirms that elevated Lp(a) concentrations are an independent factor in ASCVD, as has been demonstrated in recent years (29).

A final striking result is the worse prognosis of subjects with HyperLpa once studied in the Lipid Unit. This is probably due, on the one hand, to the excellent prognosis of subjects with primary hypercholesterolemia who receive intensive and early treatment (30). In subjects with HeFH whose only risk factor is elevated LDLc, early correction drastically reduces their risk, and our data confirm the good prognosis observed in other treated HeFH cohorts (31). However, this increased risk in HyperLpa subjects may also be due to the reduced benefit of conventional lipid-lowering therapy in subjects with very elevated Lp(a). The ongoing clinical trials with antisense oligonucleotides (32) and RNA interference against Lp(a) (33,34) will determine the benefit of this reduction.

Our study has several limitations. Lipid-lowering treatment may not have been homogeneous between subjects before and after the study in the Lipid Unit. Subjects with HeFH, having a higher familial burden of ASCVD and higher LDLc concentrations, likely received earlier and more intensive treatment. This is unlikely after their study in the Lipid Unit, where a protocol based on ASCVD risk regardless of

etiology is followed, although in recent years HeFH patients have had easier access to PCSK9 inhibitors than the rest. Actually, most genetic studies have been performed long after the start of treatment in the Unit. Our study is an observational study with retrospective data; therefore, its interpretation with respect to causality should be taken with caution. Although the mean age of participants is 50 years, we cannot exclude some survivorship bias because only those participants who have survived long enough are included in the study. Finally, the percentage of subjects lost to follow-up was 5%. Although this is not a high percentage for an observational study, differential morbidity and mortality in this population could have been missed. However, most of the subjects lost to follow-up (80%) belongs to MH, which was not the main objective of this work. In summary, in more than 50% of primary hypercholesterolemia, a significant genetic component cannot be demonstrated with current techniques. Genetic hypercholesterolemia has a worse prognosis for ASCVD than non-genetic hypercholesterolemia. Among hypercholesterolemia groups with a significant genetic component, those with elevated Lp(a) have the worst ASCVD prognosis. Conventional lipid-lowering treatment for LDLc appears to be less effective in hypercholesterolemia due to HyperLpa than in other hypercholesterolemias.

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**Author Contributions**

Conceptualization, Fernando Civeira and Ana Cenarro; Formal analysis, Fernando Civeira; Investigation, Ana Bea, Ana Cenarro, Itziar Lamiquiz Moneo, Rocío Mateo-Gallego, Estíbaliz Jarauta, Irene Gracia-Rubio, Martín Laclaustra, M. Teresa Tejedor, Victoria Marco-Benedi and Fernando Civeira; Methodology, Salvador Olmos, Martin Laclaustra and Fernando Civeira; Resources, Fernando Civeira; Writing – original draft, Fernando Civeira.

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**Table 1**. Baseline clinical characteristics and comorbidities of subtypes of hypercholesterolemia

| | HeFH | HyperLpa | PH | HyperLpa+PH | MH | IPH | Total |
|---|---|---|---|---|---|---|---|
| Sample Size, n | 400 | 181 | 434 | 128 | 1562 | 769 | 3474 |
| Prevalence, % | 11.5 | 5.2 | 12.5 | 3.7 | 45.0 | 22.1 | 100 |
| Prevalence within PI, %* | 16.5 | 7.5 | 17.9 | 5.3 | 21.1 | 31.7 | 100 |
| Age, years | 45.2 (14.9) | 52.8 (13.2) | 51.6 (11.9) | 54.4 (11.8) | 49.2 (14.1) | 51.7 (12.2) | 50.0 (13.6) |
| Women, n (%) | 226 (56.5) | 99 (54.7) | 230 (53.0) | 81 (63.3) | 727 (46.5) | 402 (52.3) | 1765 (50.8) |
| Total cholesterol, mg/dL | 372 (70.4) | 299 (24.2) | 306 (35.1) | 311 (43.2) | 256 (38.5) | 308 (33.6) | 292 (56.1) |
| Triglycerides, mg/dL | 124 (64.9) | 160 (76.7) | 165 (85.5) | 149 (76.4) | 157 (85.2) | 154 (78.1) | 153 (81.6) |
| HDL cholesterol, mg/dL | 57.3 (16.4) | 59.0 (15.6) | 57.5 (15.2) | 62.5 (18.8) | 55.7 (17.8) | 59.1 (16.1) | 57.3 (17.0) |
| LDL cholesterol, mg/dL | 290 (68.4) | 208 (22.9) | 216 (31.7) | 219 (36.4) | 169 (33.3) | 218 (29.8) | 204 (53.8) |
| Non-HDL cholesterol, mg/dL | 314 (70.8) | 240 (20.0) | 249 (32.2) | 249 (38.7) | 201 (35.5) | 249 (30.3) | 234 (53.7) |
| Apolipoprotein B, mg/dL | 183 (45.1) | 161 (28.6) | 162 (32.3) | 171 (38.2) | 134 (28.3) | 159 (30.6) | 152 (36.2) |
| Lipoprotein(a), mg/dL | 30.0 (11.4-69.9) | 166 (132-233) | 23.2 (7.9-50.2) | 144 (118-182) | 26.4 (9.8-67.5) | 25.5 (10.9-57.2) | 31.4 (11.1-78.6) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Body mass index, kg/m$^2$ | 25.5 (4.4) | 26.7 (4.2) | 27.2 (4.2) | 26.2 (3.8) | 27.4 (4.8) | 25.2 (2.9) | 26.6 (4.3) |
| Active smokers, n (%) | 107 (26.8) | 41 (22.7) | 108 (24.9) | 20 (15.6) | 344 (22.0) | 198 (25.7) | 818 (23.5) |
| Diabetes, n (%) | 12 (3.0) | 13 (7.3) | 24 (5.5) | 7 (5.5) | 180 (11.8) | 0 | 236 (7.0) |
| Hypertension, n (%) | 69 (17.6) | 47 (27.3) | 124 (28.6) | 35 (27.6) | 452 (31.2) | 170 (26.3) | 897 (27.8) |
| ASCVD, n (%) | 36 (9.0) | 34 (18.8) | 38 (8.8) | 17 (13.3) | 139 (8.9) | 43 (5.6) | 307 (8.8) |
| Family history of premature ASCVD, n (%) | 131 (34.8) | 48 (28.6) | 95 (22.3) | 31 (24.8) | 275 (19.3) | 134 (20.9) | 714 (22.6) |
| Polygenic risk score | 0.917 (0.199) | 0.889 (0.147) | 1.155 (0.076) | 1.149 (0.072) | 0.879 (0.154) | 0.899 (0.142) | 0.977 (0.184) |

HeFH denotes heterozygous familial hypercholesterolemia; HyperLpa, hyperlipoproteinemia (a); PH, polygenic hypercholesterolemia; MH, multifactorial hypercholesterolemia; IPH, idiopathic primary hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ASCVD, atherosclerotic cardiovascular disease

Quantitative variables are expressed as mean (standard deviation), except for variables not following normal distribution ((lipoprotein (a)), expressed as median (interquartile range). Qualitative variables are expressed as total number (n) and percentage (%).

* Prevalence within PI refers to the percentage of subjects within the group of subjects with primary hypercholesterolemia (n=2429), which includes probands with LDLc ≥190 mg/dL or non-HDLc ≥220 mg/dL or LDLc ≥130 mg/dL or non-HDLc ≥160 mg/dL with strong family history of hypercholesterolemia.

**Table 2.** Variables associated in the Cox regression analysis with a first event of ASCVD from birth

| | B | P | Exp(B) | 95% CI for Exp(B) | |
|---|---|---|---|---|---|
| | | | | Low | High |
| Gender, woman | -1.118 | 0.000 | 0.327 | 0.253 | 0.424 |
| Family history of precocious ASCVD, yes | 0.376 | 0.001 | 1.456 | 1.163 | 1.823 |
| Diabetes, yes | 0.489 | 0.001 | 1.631 | 1.231 | 2.161 |
| Hypertension, yes | 0.332 | 0.002 | 1.394 | 1.128 | 1.721 |
| HDL cholesterol, mg/dL | -0.025 | 0.000 | 0.975 | 0.967 | 0.983 |
| Polygenic risk score | 0.704 | 0.042 | 2.021 | 1.025 | 3.985 |
| LogLpa | 0.005 | 0.000 | 1.005 | 1.004 | 1.007 |
| Smoking, former or current | 0.730 | 0.000 | 2.075 | 1.617 | 2.664 |

ASCVD denotes atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LogLpa, logarithm lipoprotein(a)

Variables included in the regression model without statistical significance: triglycerides, body mass index, LDL cholesterol.

**Table 3**. Variables independently associated with ASCVD during the follow-up in the Cox regression analysis.

| | | | | 95% CI for Exp(B) | |
|---|---|---|---|---|---|
| | B | P | Exp(B) | Low | High |
| Age at baseline, year | 0.044 | 0.000 | 1.045 | 1.029 | 1.062 |
| ASCVD at baseline, yes | 1.150 | 0.000 | 3.157 | 2.208 | 4.514 |
| Sex, woman | -0.528 | 0.006 | 0.590 | 0.404 | 0.860 |
| Diabetes, yes | 0.588 | 0.005 | 1.801 | 1.198 | 2.707 |
| Hypertension, yes | 0.568 | 0.001 | 1.764 | 1.269 | 2.453 |
| HDL cholesterol, mg/dL | -0.013 | 0.053 | 0.987 | 0.975 | 1.000 |
| LogLpa | 0.003 | 0.014 | 1.003 | 1.001 | 1.005 |
| Smoker at baseline, yes | 0.350 | 0.048 | 1.419 | 1.003 | 2.007 |

ASCVD denotes atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LogLpa, logarithm lipoprotein(a)

Variables included in the regression model without statistical significance: triglycerides, body mass index, LDL cholesterol, polygenic risk score.

**Figure legends**

**Figure 1. Flowchart of the study and frequency of the different hypercholesterolemia subgroups**

**Figure 1 legend**

LDLc denotes low-density lipoprotein cholesterol; HDLc. high-density lipoprotein cholesterol; Lp(a). lipoprotein (a); PRS. polygenic risk score; HyperLp(a). hyperlipoproteinemia (a); PH. polygenic hypercholesterolemia; MH. multifactorial hypercholesterolemia; IPH. idiopathic primary hypercholesterolemia; VUS. genetic variant of uncertain significance.

Strong family history includes the presence of a first-degree relative with primary LDLc ≥190 mg/dL.

Monogenic criteria include: tendon xanthomas in the proband or first degree relative, or in the presence of LDLc ≥220 mg/dL if age <40 years or ≥230 mg/dL if age ≥40 years) in the proband or in a first-degree relative plus dominant hypercholesterolemia pattern with vertical transmission in multigenerational pedigrees, and approximately 50% affected first degree relatives with only one affected parent.

*Of the 63 subjects with genetic variants of uncertain significance (VUS). 9 had HyperLpa criteria. 25 had PH criteria. and 6 had both. The remaining 23 subjects were classified as having HeFH.

**Figure 2.** Kaplan-Meier survival curves of ASCVD from birth: Panel A, according to the subgroup of hypercholesterolemia; Panel B, hypercholesterolemia of the genetic origin versus non-genetic hypercholesterolemia; Panel C, hypercholesterolemia of the genetic origin versus idiopathic hypercholesterolemia; Panel D, among genetic subgroups of genetic hypercholesterolemia.

**Figure 3**. Kaplan-Meier survival curves of ASCVD from the beginning of the study in the Lipid Unit divided by subgroup of hypercholesterolemia

**Figure 4.** Kaplan-Meier survival curves of ASCVD from the beginning of the study in the Lipid Unit in subjects with and without HyperLpa.