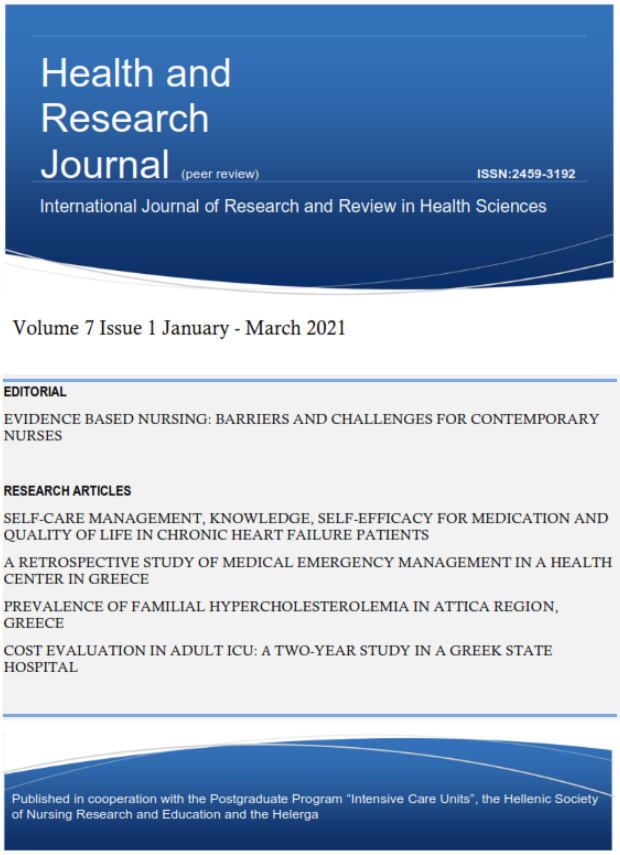
Health & Research Journal

Vol 7, No 1 (2021)

Volume 7 Issue 1 January-March 2021



Prevalence of familial hypercholesterolemia in Attica region, Greece

Niki Pavlatou, Nikoletta Rovina, Georgia Toylia, Olga Kadda, Christina Marvaki, Theodore Kapadochos, Genovefa Kolovou, Antonia Koutsoukou

doi: 10.12681/healthresj.26096

HEALTH AND RESEARCH JOURNAL
E-ISSN:2459-3192

(2021), Volume 7, Issue 1

RESEARCH ARTICLE

PREVALENCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN ATTICA REGION, GREECE

Niki Pavlatou[1], Nikoletta Rovina[2], Georgia Toylia[3], Olga Kadda[4], Christina Marvaki[5], Theodore Kapadochos[3], Genovefa Kolovou[6], Antonia Koutsoukou[7]

1. Lecturer, Department of Nursing, University of West Attica, Greece
2. Assistant Professor, Intensive Care Unit, 1st Department of Respiratory Medicine, National and Kapodistrian University of Athens, "Sotiria" Chest Disease Hospital, Athens, Greece
3. Assistant Professor, Department of Nursing, University of West Attica, Athens, Greece
4. RN, PhD, Cardiac Intensive Care Unit, Onassis Cardiac Surgery Center, Greece
5. Emeritus Professor, Department of Nursing, University of West Attica, Greece
6. MD, Director of Preventive Cardiology, Lipid Disorders Clinic and LA Unit, Metropolitan Hospital, Greece
7. Professor ICU, National and Kapodistrian University of Athens, 1st Dept of Respiratory Medicine, "Sotiria" Chest Disease Hospital, Athens, Greece

Abstract

Background: Dyslipidemias are one of the major modifiable risk factors for cardiovascular disease. Familial hypercholesterolemia (FH) is the most common genetic metabolic disorder; it is estimated that around 14-34 million people worldwide have FH but only 25% of FH patients have been diagnosed.
Aim: The aim of the present study was to explore the prevalence of FH in Attica region, Greece.
Methods: Attica region was divided into 8 regional units. A predesigned questionnaire was used to collect demographic and clinical data. Data analysis was performed by using the Statistical Package for the Social Sciences (SPSS), ver. 20.
Results: The studied sample consisted of 1578 Greek inhabitants of Attica region. The majority of the sample was women (59.9%). The mean age of the studied participants was 47.1 (±14.9) years. According to Simon Broome criteria, the probability of an FH diagnosis as unlikely is determined in 98.7% of the studied sample, probable in 0.8% of the participants or definite in 0.5% of the participants, based on this data, the prevalence of FH in Attica region, Greece is 1:200. Qualitative factors found to be associated with the onset of the disease were medication (p-value = 0.001) and hypolipidemic therapy (p-value = 0.001). The quantitative factors found to be associated with disease onset were body mass index (p-value = 0.044), and systolic (p-value = 0.001) and diastolic (p-value = 0.007) pressure.
Conclusions: Based on our data, the prevalence of FH in Attica region, Greece is 1:200. Early identification of contributing factors in FH development and proper treatment is vital and reduce the risk of premature and severe atherosclerotic disease.

Keywords: Familial hypercholesterolemia, prevalence, risk, cardiovascular disease.

CorrespondingAuthor: Niki Pavlatou, Zichnis street 19, PC 11527, Athens, Greece. Mobile number:+306937155068, Email: npavlatou@uniwa.gr

Cite as: Pavlatou, N., Rovina, N., Toylia, G., Kadda, O., Marvaki, C., Kapadochos, T., Kolovou, G., Koutsoukou, A., (2021). Prevalence of familial hypercholesterolemia in Attica region, Greece. Health and Research Journal,7(1),26-38. https://ejournals.epublishing.ekt.gr/index.php/HealthResJ

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide and their numbers are expected to increase in the coming years.[1]

The problems that affect the circulatory system derive from atherosclerosis. Atherosclerosis is a chronic inflammatory condition in large and middle-sized arteries, where activated immune competent cells are abundant and as a consequence plaque rupture may be triggered.[2,3]

The presence of atherosclerosis is evidenced across various geographic regions, cultures and lifestyles.[4]

According to Euro stat, the death rate for cardiovascular disease was 258 deaths per 100.000 inhabitants in 2016 in both high and low-income countries.[5]

CVD mortality rates in Greece have decreased during the last 15 years, a fact that could be partially attributed to the lower prevalence of smoking and the increase in physical activity among the Greek population.[6] According to data from the Hellenic Statistical Authority (ELSTAT), developed by the Institute for Economic and Industrial Research (IOBE), which cover the period 2000 - 2012, there are significant changes in the causes of death in Greece. Vlachadis et al.,[7] analyzed official national data for causes of death in Greece concerning the period 2004–2012 and they concluded that the decreasing trends in CVD mortality, being witnessed in the pre-crisis period, remained unaffected during the years of the crisis (2008–2012).

Dyslipidemias are one of the major modifiable risk factors for cardiovascular disease. Familial hypercholesterolemia (FH - Familial Hypercholesterolemia) belongs to the primary dyslipidemias in which defective genes disrupt the metabolic pathway of lipid and sterol clearance. FH is the most common genetic metabolic disorder and one of the few underlying genetic disorders known as dyslipidemia. It is estimated that around 14-34 million people worldwide have FH but only 25% of FH patients have been diagnosed.[8]

The disease is mainly due to low density lipoprotein (LDL) receptor gene mutations, which cause reduced functionality or reduced receptor production, resulting in decreased catabolism of LDLs and their accumulation in plasma. The disease is inherited mainly with autosomal dominant nature. The frequency of heterozygotes is 1: 500 in the general population (in some populations it is reported 1: 200 and even lower) and in homozygotes 1: 1,000,000 (in some populations it is reported 1: 600 000).[9]

The true prevalence of FH in Greece is unknown, but it is estimated that there are at least 40,000 FH patients nationwide pointing to a prevalence of 1:250. The overwhelming majority of 90% remain undiagnosed.[10]

Therefore, prompt detection of these patients is of pivotal importance in order to implement appropriate preventive measures at a young age. National registries of FH patients have been a success in other countries such as Netherlands and Spain, as they are proved to be a significant tool for promoting best clinical practices. As Greece did not have a national FH registry, the Hellenic College of Treatment of Atherosclerosis (HCTA) create the National Familial Hypercholesterolemia Registry (GRegistry-FH, ClinicalTrials.gov Identifier: NCT03140605.[11,12]

Thus, the purpose of t the present article is to provide data related to the prevalence of FH in the Attica region.

MATERIAL AND METHODS

GRregistry-FH, Rationale

The HCTA (a non-profit scientific organization) has established the national registry GRregistry-FH with ClinicalTrials.gov Identifier: NCT03140605. The primary purpose of the GRregistry-FH is to collate data to facilitate clinical service planning and to inform clinical best practices.[11]

Study design

An epidemiological study was conducted between November 2016 and December 2019.

Participants

One thousand five hundred seventy-eight (1578) inhabitants of Attica region, Greece, were included in the study. The Attica region was divided into 8 regional units, according to the size of population which was based on the latest Hellenic General Population Census, Hellenic Statistical Authority, ELSTAT year 2011. An appropriate number of interviewers were determined. The inclusion criteria of the participants were age >18 years old and the ability to sign an informed consent. The exclusion cri-

terion was the denial of an informed consent.

Questionnaire

A predesigned questionnaire was used to collect demographic and anthropometric characteristics, such as age, gender, height, body weight, body mass index [BMI- was calculated as weight (kg) / height2 (cm)]. Moreover, medical information was recorded such as history and management of hypertension; participants who had blood pressure levels ≥140/90 mmHg or used antihypertensive drugs were classified as hypertensive, according to the latest guidelines. Additionally, history of diabetes mellitus was recorded (fasting blood glucose> 126 mg / dL or/and usage of antidiabetic drugs or insulin). History of hypercholesterolemia was also included in the questionnaire; it was defined as (fasting) blood lipids levels over 200 mg/dL and by patient's use of lipid-lowering agents. It was also recorded family medical history of CVD or related comorbidities (i.e thyroid disease).

Smoking status was assessed; current smokers were defined as those who smoked at least on cigarette per day, former smokers as those who quit smoking for more than one year. The number of cigarettes per day and smoking years was also recorded. As for the participants' dietary habits, fish consumption per week was also taken into consideration. Alcohol consumption was defined as a glass of wine (100ml) (1-2 glasses / day). Small consumption <3 glasses of wine / day, moderate consumption 3-6 glasses of wine / day, heavy consumption > 7 glasses / day.

Physical activity was assessed by recording the frequency (how many times/week) and duration (≥20 minutes/per time).

Criteria for FH diagnosis

Simon Broome Register criteria for FH diagnosis were used according to high cholesterol levels, manifestation of premature Atherosclerotic Cardiovascular Disease (ASCVD), and presence of tendon xanthomas in individuals and in their first-degree family members.[13]

Ethics

All individuals enrolled on a volunteer basis so as the study purpose, design and workflow were explained to each participant. A written informed consent was obtained from each participant and before the interviewer filled in the questionnaire. A door-to-door research method was applied. Ethical approval from national organization of medicines was obtained, (97783/20-12-2016).

Statistical analysis

Continuous variables are presented as mean values ± standard deviation and categorical variables as frequencies. X^2 independence test or Fisher's exact test -where necessary- were used to identify possible quality factors associated with the occurrence of familial hypercholesterolemia. Also, Student's t-test as well as non-parametric Mann-Whitney test was used to test for a correlation between a quantitative risk factor and the incidence of the disease. The level of statistical significance was set at a = 5%. Data analysis was performed using SPSS ver. 20 (SPSS Inc, Chicago, Il, USA).

RESULTS

The present study involved 1849 Greek inhabitants of Attica region, excluding 271 participants, as there was no information on the Simon Broome criteria used to diagnose FH. Therefore, the studied sample consisted of 1578 Greek inhabitants of Attica region. The demographic, anthropometric and lifestyle characteristics of the studied sample are presented in ***Table 1.*** The majority of the sample was women (59.9%). The mean age of the studied participants was 47.1 (±14,9) years. In *Table 2,* the results of the data analysis according to clinical characteristics of the studied sample are presented. According to Simon Broome criteria, the probability of an FH diagnosis as unlikely is determined in 98.7% of the studied sample, probable in 0.8% of the participants or definite in 0.5% of the participants, based on this data, the prevalence of FH in Attica region, Greece is 1:200. Family history of the studied sample is presented in *Table 3*.

In *Tables 4, 5 and 6*, factors associated with FH are presented. Qualitative factors found to be associated with disease onset were medication (p-value = 0.001) and hypolipidemic therapy (p-value = 0.001) (Table 4). In more detail, we note the following:

People who take medication have a higher rate of FH compared to people who do not take any medication (1.4% vs

0.0%). People taking hypolipidemic therapy have a higher rate of FH compared with people who do not receive this treatment (6.3% vs 0.0%) (Table 5).

The quantitative factors found to be associated with disease onset were body mass index (p-value = 0.044), and systolic (p-value = 0.001) and diastolic (p-value = 0.007) blood pressure (Table 6). Specifically, we observe the following:

People with a definite diagnosis of FH have a higher body mass index (median 28.1 vs 25.0). In terms of systolic and diastolic blood pressure, people with FH show higher measurements than people who do not have disease (median 140.0 vs 120.0 and median 80.0 vs 70.0 respectively).

DISCUSSION

In the present study, was described the prevalence of FH in 1578 inhabitants of Attica region in Greece. Factors found to be related to the onset of the disease were medication, hypolipidemic therapy, body mass index (p-value = 0.044), systolic and diastolic blood pressure. These data are in accordance or inconsistent with recently published studies.[14-20]

Wang et al.,[21] in their study, identified that overweight/obesity was positively associated with FH. Moreover, Thavendiranathan et al.,[22] in their study found that people with higher BMI scores significantly correlated with high triglyceride levels. The study revealed no association between patients' physical activity levels and lipid profile or BMI.

Several clinical risk factors are significantly and independently associated with cardiovascular risk in patients with FH; therefore should be targeted for modification. There are studies that reveal a strong relation between factors such as myocardial infraction, diabetes mellitus and FH but in our study these factors were not related to FH. According to Cui et al.,[23] FH is a genetic cause of premature myocardial infarction. In their study, they found that prevalence of FH among patient with premature myocardial infraction appeared relatively common. Besseling et al.,[24] found that prevalence of diabetes mellitus was significantly lower in patients with FH than in their unaffected relatives.

Although FH is one of the most common genetic disorders, it remains largely underdiagnosed and undertreated. Few years ago, the Hellenic Atherosclerosis Society has established the Hellenic Familial Hypercholesterolemia Registry, part of the Familial Hypercholesterolemia Studies Collaboration (FHSC), to evaluate the characteristics and management of patients with FH in Greece. The conclusion derived from this study was that FH in Greece is characterized by a significant delay in diagnosis and a high prevalence of both family and personal history of established CVD.[25]

A recent study of Dumitrescu et al.,[26] described the prevalence of FH in Romania by applying the Dutch Lipid Clinic Network (DLCN) criteria. The sample studied consisted of 59 patients, out of whom 61% were females. According to their results, 91.52% of the patients had a possible FH, while 6.7% had a probable FH and 1.6% a definite FH diagnosis; thus, the prevalence of FH in Romania is: 1:213.

Another study conducted by Benn et al.,[27] in Copenhagen, found that the prevalence of FH in 98,098 participants, was 1:217 in the general population.

The prevalence of FH used to be reported as 1 in 500. European reports suggest a higher prevalence; the US FH prevalence is unknown. A study reported by de Ferranti et al.,[28] refers to differences by age, gender, race or ethnicity so as obesity status. Their results in relation to obesity status came in accordance to our results; more obese participants qualified as definite FH than non-obese. The researchers underline that variations in prevalence by age and obesity status suggest that clinical criteria may not be sufficient to estimate FH prevalence.

Limitations

The main limitation of the present study was participants' ability to report accurately their family history and their lifestyle habits.

CONCLUSIONS

In conclusion, FH is a common and treatable disorder; early diagnosis and treatment will improve clinical cardiovascular outcomes. As the vast majority of FH patients may confront serious problems with compliance to medical treatment or lifestyle modification, strategies to improve awareness and management of FH are definitely needed. Based on this data, the prevalence of FH in Attica region, Greece is 1:200.

Conflict of interest

The authors declare no conflict of interest in regard to contents of this article

REFERENCES

1. Heidenreich P, Trogdon, J.G., Khavjou, O.A., Butler, J., Dracup, K., Ezekowitz, M.D., et al. Forecasting the future of cardiovascular disease in the U.SA: A policy statement from American Heart Association. Circulation. 2011;123:933-9442.
2. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med. 2013;11:117.
3. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, Tang D, Chen R. Research Progress on the Relationship between Atherosclerosis and Inflammation. Biomolecules. 2018;8:80.
4. Ndrepepa G. Atherosclerosis & ischaemic heart disease: Here to stay or gone tomorrow.Indian J Med Res. 2017;146:293-297.
5. On line: Statistics Explained. https://ec.europa.eu/eurostat/statisticsexplained/. Last accessed: 28/11/2019.
6. Michas G, Karvelas G, Trikas A. Cardiovascular disease in Greece; the latest evidence on risk factors. Hellenic J Cardiol. 2019;60:271-275.
7. Vlachadis N, Iliodromiti Z, Vlachadi M, Xanthos T, Ktenas E, Vrachnis D, Kornarou E, Vrachnis N. Cardiovascular mortality and the financial crisis in Greece: trends and outlook. Int J Cardiol. 2014;176:1367-8.
8. Pejic RN. Familial hypercholesterolemia.Ochsner J. 2014;14:669-72.
9. Ramasamy I.Update on the molecular biology of dyslipidemias.Clin Chim Acta. 2016;454:143-85.
10. Pitsavos C, Panagiotakos DB, Chrysohoou C, Stefanadis C. Epidemiology of cardiovascular risk factors in Greece: aims, design and baseline characteristics of the ATTICA study. BMC Public Health. 2003;3:32.
11. Kolovou G, Marvaki C, Makrygiannis S, Kadda O, Giannakopoulou V, Kalogeropoulos P, et al. Rationale and design of the Greek registry for familial hypercholesterolemia (GRegistry-FH) of the hellenic college of treatment of atherosclerosis (HCTA). Hellenic J Cardiol. 2019:S1109-9666(19)30281-7.
12. Rizos CV, Athyros V, Bilianou E, Chrousos G, Garoufi A, Kolovou G, et al. An insight into familial hypercholesterolemia in Greece: rationale and design of the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). Hormones (Athens). 2017;16:306-312.
13. Al-Rasadi K, Al-Waili K, Al-Sabti HA, Al-Hinai A, Al-Hashmi K, Al-Zakwani I, et al.Criteria for Diagnosis of Familial Hypercholesterolemia: A Comprehensive Analysis of the Different Guidelines, Appraising their Suitability in the Omani Arab Population.Oman Med J. 2014;29:85-91.
14. Brunham LR, Ruel I, Khoury E, Hegele RA, Couture P, Bergeron J, et al.Familial hypercholesterolemia in Canada: Initial results from the FH Canada national registry.Atherosclerosis. 2018;277:419-424.
15. Béliard S, Boccara F, Cariou B, Carrié A, Collet X, Farnier M, et al; French FH Registry group.High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry.Atherosclerosis. 2018;277:334-340.
16. Kayikcioglu M, Tokgozoglu L, Dogan V, Ceyhan C, Tuncez A, Kutlu M, et al.What have we learned from Turkish familial hypercholesterolemia registries (A-HIT1 and A-HIT2)?Atherosclerosis. 2018;277:341-346.
17. Schmidt N, Dressel A, Grammer TB, Gouni-Berthold I, Julius U, Kassner U, et al.Lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients with familial hypercholesterolemia in Germany: The CaRe-High Registry.Atherosclerosis. 2018;277:314-322.
18. Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, Dominguez F, Quintana L, Lluís-Ganella C, et al. J Am Coll Cardiol. 2017; 70(14):1732-1740.
19. Pirazzi C, Håkansson L, Gustafsson C, Omerovic E, Wiklund O, Mancina RM.High prevalence of genetic determined familial hypercholesterolemia in premature coronary artery disease.Appl Clin Genet. 2019;12:71-78.
20. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercho-

lesterolemia: a HuGE prevalence review.Am J Epidemiol. 2004;160(5):407-20.

21. Wang Y, Li Y, Liu X, Tu R, Zhang H, Qian X, et al. The prevalence and related factors of familial hypercholesterolemia in rural population of China using Chinese modified Dutch Lipid Clinic Network definition. BMC Public Health. 2019;19:837.
22. Thavendiranathan P, Jones E, Han RK, Cullen-Dean G, Helden E, Conner WT, et al. Association between physical activity, adiposity, and lipid abnormalities in children with familial hyperlipidemia. Eur J Cardiovasc Prev Rehabil. 2007;14:59-64.
23. Cui Y, Li S, Zhang F, Song J, Lee C, Wu M, Chen H. Prevalence of familial hypercholesterolemia in patients with premature myocardial infarction. Clin Cardiol. 2019;42:385-390.
24. Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. JAMA. 2015;313(10):1029-1036.
25. Rizos CV, Elisaf MS, Skoumas I, Tziomalos K, Kotsis V, Rallidis L, et al. Characteristics and management of 1093 patients with clinical diagnosis of familial hypercholesterolemia in Greece: Data from the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH).Atherosclerosis. 2018;277:308-313.
26. Dumitrescu A, Mosteoru S, Vinereanu D, Dan GA, Gaita L, Gaita D. Preliminary data of familial hypercholesterolemia (FH) patients in Romania. Atherosclerosis. 2018;277:304-307.
27. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217.Eur Heart J. 2016;37:1384-94.
28. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES).Circulation. 2016;133:1067-72.

ANNEX

Table 1 . Demographic, anthropometric and lifestyle characteristics of the studied sample.

N=1578	**N (%)**
Gender	
Men	632 (40.1%)
Women	946 (59.9%)
Women >55 years old	
No	735 (77.9%)
Yes	208 (22.1%)
Men >45 years old	
No	290 (46.1%)
Yes	339 (53,9%)
Alcohol consumption	
No	427 (27,2%)
Small 3</24h	923 (58.9%)
Moderate 3-6/24h	204 (13.0%)
Heavy > 7/24h	13 (0.8%)
Exercise (> 20 minutes) / week	
At all	208 (13.3%)
1 time	476 (30.5%)
2 times	326 (20.9%)
3 times	249 (15.9%)
4 times	304 (19.4%)
Fish consumption / week	
At all	113 (7.2%)
1 time	848 (54.0%)
2 times	408 (26.0%)
3 times	121 (7.7%)
4 times	79 (5.0%)
Smoking	
No	986 (63.0%)
Cessation >1 year	96 (6.1%)
Yes	484 (30.9%)
Electronic cigarette	
No	1519 (97.5%)
Yes	39 (2.5%)
Obesity status	
Underweight	31 (2.0%)
Normal weight	750 (48.0%)

Overweight	516 (33.0%)
Obese (mild)	192 (12.3%)
Obese (moderate)	54 (3.5%)
Obese (severe)	20 (1.3%)
	Mean (S.D.)
Age (years)	47.1 (14.9)
	Median
	(Interquartile range)
Height (cm)	169.0 (162.0-175.0)
Weight (Kg)	72.0 (62.0-84.0)
BMI (kg/m^2)	25.0 (22.8-28.1)
Systolic blood pressure (mmHg)	120.0 (110.0-130.0)
Diastolic blood pressure (mmHg)	70.0 (70.0-80.0)
Cigarette packet	1.0 (0.5-1.0)
Years of smoking	20.0 (15-30)

S.D.: Standard Deviation

Table 2. Clinical characteristics of the studied sample

	N (%)
Drugs	
No	1001 (63.9%)
Yes	565 (36.1%)
Xanthomas	
No	1527 (97.0%)
Yes	48 (3.0%)
Arcus Cornile	
No	1553 (98.7%)
Yes	20 (1.3%)
Tentom xanthomas	
No	1559 (99.2%)
Yes	13 (0.8%)
Xanthoma detection	
Achilleus	2 (15.4%)
Hands	5 (38.5%)
Knee	6 (46.2%)
Blood pressure	
No	1312 (83.2%)
Yes (>140/90 or drugs)	265 (16.8%)
Diabetes mellitus	
No	1481 (94.0%)
Yes (>126mg/dL or drugs)	95 (6.0%)
Lipid-lowering agents	
No	1441 (91.4%)
Yes	135 (8.6%)
Coronary artery disease	
No	1531 (97.3%)
Yes	42 (2.7%)
Myocardial infarction	
No	1537 (97.7%)
Yes	36 (2.3%)
Stroke	
No	1512 (96.1%)
Yes	61 (3.9%)
Hypothyroidism	
No	1297 (85.8%)
Yes	215 (14.2%)
Hyperthyroidism	
No	1481 (97.9%)
Yes	32 (2.1%)
Classification for FH (according Simon Broome criteria)	
No disease	1557 (98,7%)
Probable diagnosis	13 (0,8%)
Definite diagnosis	8 (0,5%)

Table 3. Family history of the studied sample.

	N (%)
Relatives with high cholesterol	
No	511 (34.0%)
Yes	992 (66.0%)
1	612 (61.7%)
2	262 (26.4%)
3	66 (6.7%)
4	52 (5.2%)
Family history of coronary artery disease	
No	1071 (68.0%)
Yes	503 (32.0%)
Family history of stroke	
No	1136 (72.2%)
Yes	437 (27.8%)
Relatives > 90 years old	
No	1036 (65.9%)
Yes	535 (34.1%)
1	343 (64.6%)
2	122 (23.0%)
3	48 (9.0%)
4	18 (3.4%)

Table 4. Qualitative factors related to prevalence of familial hypercholesterolemia and participants' habits so as the clinical characteristics of the participants related to the occurrence of familial hypercholesterolemia

	Familial hypercholesterolemia		
	No disease	Condident Diagnosis	
	N(%)	**N(%)**	**p-value**
Gender			0.066
Men	621(99.0%)	6(1.0%)	
Women	937(99.8%)	2(0.2%)	
Women >55 years old			0.999
No	730(99.7%)	2(0.3%)	
Yes	204(100.0%)	0(0.0%)	
Gender			0.692
Men	286(99.3%)	2(0.7%)	
Women	332(98.8%)	4(1.2%)	
Alcohol consumption			0.400
No	420(99.8%)	1(0.2%)	
Small 3</24h	915(99.6%)	4(0.4%)	
Moderate 3-6/24h	213(99.1%)	2(0.9%)	
Exercise (> 20 minutes) / week			0.999
At all	202(99.5%)	1(0.5%)	
1-2 times	794(99.5%)	4(0.5%)	
3-4 times	547(99.5%)	3(0.5%)	
Fish consumption / week			0.272
At all	110(99.1%)	1(0.9%)	
1 time	834(99.3%)	6(0.7%)	
2 times	407(100.0%)	0(0.0%)	
3-4 times	198(99.5%)	1(0.5%)	
Obesity status			0.150
Underweight / Normal weight	775(99.7%)	2(0.3%)	
Overweight	508(99.4%)	3(0.6%)	
Obese $1^{st}/2^{nd}/3^{rd}$ degree	260(98.9%)	3(1.1%)	
Smoking			0.082
No	978(99.8%)	2(0.2%)	
Cessation >1 year	94(98.9%)	1(1.1%)	
Yes	474(99.0%)	5(1.0%)	
Electronic cigarette			0.071
No	1500(99.5%)	7(0.5%)	
Yes	38(97.4%)	1(2.6%)	

Table 5. Qualitative factors related to the clinical characteristics of the participants and related to the occurrence of familial hypercholesterolemia

	Familial hypercholesterolemia		
	No disease	Condident Diagnosis	
	N(%)	**N(%)**	**p-value**
Drugs			**0.001**
No	998(100.0%)	0(0.0%)	
Yes	548(98.6%)	8(1.4%)	
Blood pressure			0.132
No	1301(99.6%)	5(0.4%)	
Yes (>140/90 or drugs)	256(98.8%)	3(1.2%)	
Diabetes mellitus			0.999
No	1462(99.5%)	8(0.5%)	
Yes (>126mg/dL or drugs)	94(100.0%)	0(0.0%)	
Lipid-lowering agents			**0.001**
No	1436(100.0%)	0(0.0%)	
Yes	120(93.8%)	8(6.3%)	
Coronary artery disease			0.192
No	1513(99.5%)	7(0.5%)	
Yes	40(97.6%)	1(2.4%)	
Myocardial infarction			0.166
No	1519(99.5%)	7(0.5%)	
Yes	34(97.1%)	1(2.9%)	
Stroke			0.999
No	1494(99.5%)	8(0.5%)	
Yes	59(100.0%)	0(0.0%)	
Hypothyroidism			0.147
No	1287(99.8%)	3(0.2%)	
Yes	209(99.1%)	2(0.9%)	
Hyperthyroidism			0.999
No	1465(99.7%)	5(0.3%)	
Yes	32(100.0%)	0(0.0%)	

Table 6. Quantitative factors associated with the occurrence of familial hypercholesterolemia

	Familial hypercholesterolemia				
	No disease		Possible/Condident Diagnosis		
	N	**Mean (S.D.)**	**N**	**Mean (S.D.)**	**p-value**
Age (years)	1551	47,1 (15,0)	8	54,6 (12,7)	0,129
	N	**Median (Interquartile range)**	**N**	**Median (Interquartile range)**	
BMI (kg/m^2)	1543	25.0(22.7-28.0)	8	28.1(25.6-31.2)	**0.044**
Cigarete package per day	415	1.0(0.5-1.0)	5	1.0(1.0-1.5)	0.181
Smoking years	461	20.0(14.0-30.0)	6	30.0(28.0-35.0)	0.099
Systolic blood pressure (mmHg)	1474	120.0(110.0-130.0)	8	140.0(130.0-150.0)	**0.001**
Diastolic blood pressure (mmHg)	1466	70.0(70.0-80.0)	8	80.0(80.0-90.0)	**0.007**
Blood glucose	1371	90.0(84.0-100.0)	7	90.0(82.0-110.0)	0.741
Triglycerides without medication treatment	1541	120.0(86.0-149.0)	8	135.0(100.0-234.5)	0.163
HDL without medication treatment	1555	50.0(46.0-61.0)	8	63.0(47.7-80.0)	0.179
Triglycerides with medication treatment	109	115.0(85.0-150.0)	8	100.5(68.5-135.5)	0.325
HDL with medication treatment	113	48.0(40.0-60.0)	8	56.5(35.0-74.3)	0.552
Thyroid stimulating hormone	823	2.2(1.4-3.0)	5	1.2(1.0-1.2)	0.135
Relatives >90 years old	1541	0.0(0.0-1.0)	8	0.0(0.0-0.0)	0.177

S.D.= Standard Deviation