PREVALENCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN ATTICA REGION, GREECE

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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.

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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 (GRregistry-FH, ClinicalTrials.gov Identifier: NCT03140605).\(^11,12\)

Thus, the purpose of 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-
A predesigned questionnaire was used to collect demographic and anthropometric characteristics, such as age, gender, height, body weight, body mass index (BMI - 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. X² 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 infarction, 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 infarction 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.

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

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ANNEX

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

| Characteristics                      | 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/m²)                | 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.

| Relative Category                                      | 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 | Condent Diagnosis | p-value |
|-------------------------------|------------|-------------------|---------|
| **Gender**                    |            |                   |         |
| Men                           | 621 (99.0%) | 6 (1.0%)          | 0.066   |
| 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<2nd/3rd 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%)  | 2 (2.6%)          |         |
Table 5. Qualitative factors related to the clinical characteristics of the participants and related to the occurrence of familial hypercholesterolemia

|                  | No disease | Condident Diagnosis | p-value |
|------------------|------------|---------------------|---------|
| **Familial hypercholesterolemia** |            |                     |         |
| **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

| Factor                              | No disease | Possible/Confident Diagnosis | p-value |
|-------------------------------------|------------|------------------------------|---------|
|                                     | N Mean (S.D.) | Median (Interquartile range) | N Mean (S.D.) | Median (Interquartile range) |
| Age (years)                         | 1551 47.1 (15.0) | 8 54.6 (12.7)  | 0.129 |
| BMI (kg/m²)                         | 1543 25.0 (22.7-28.0) | 8 28.1 (25.6-31.2) | 0.044 |
| Cigarette 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