

## Rationale, design and preliminary results of the GALIPEMIAS study (prevalence and lipid control of familial dyslipidemia in Galicia, northwest Spain)

Rosa María Argüeso-Armesto<sup>1</sup>, Teresa-Rosalía Pérez-Castro<sup>2</sup>, José Luis Díaz-Díaz<sup>3</sup>, Avelino Rodríguez-González<sup>4</sup>, María Eugenia Ameneiros-Lago<sup>5</sup>, Alberto del Alamo-Alonso<sup>6</sup>, José Manuel de Toro-Santos<sup>7</sup>, Pablo Ángel Fernández-Catalina<sup>8</sup>, Marta Pena-Seijo<sup>9</sup>, Jose Antonio Díaz-Peromingo<sup>10</sup>, Antonio Pose-Reino<sup>11</sup>, Carlos Alberto Názara-Otero<sup>12</sup>, María Rosa Vázquez-Freire<sup>13</sup>, Lisett Escobar-Seoane<sup>14</sup>, Pedro Gordo-Fraile<sup>15</sup>, María del Mar Castellanos-Rodríguez<sup>16</sup>, José Ángel Rodríguez-Fernández<sup>17</sup>, Javier Muñiz<sup>2</sup>

<sup>1</sup> Servicio Galego de Saúde, Servicio de Endocrinología, Hospital Universitario Lucus Augusti, Lugo, Spain

<sup>2</sup> Universidade da Coruña, Grupo de Investigación Cardiovascular (GRINCAR), Instituto Universitario de Ciencias de la Salud e Instituto de Investigación Biomédica de A Coruña (INIBIC), A Coruña, Spain

<sup>3</sup> Servicio Galego de Saúde, Servicio de Medicina Interna, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain

<sup>4</sup> Servicio Galego de Saúde, Servicio de Medicina Interna, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain

<sup>5</sup> Servicio Galego de Saúde, Servicio de Medicina Interna, Hospital Arquitecto Macide, Ferrol, A Coruña, Spain

<sup>6</sup> Servicio Galego de Saúde, Centro de Atención Primaria Novoa Santos, Ourense, Spain

<sup>7</sup> Servicio Galego de Saúde, Servicio de Medicina Interna, Complejo Hospitalario Universitario de Ourense, Ourense, Spain

<sup>8</sup> Servicio Galego de Saúde, Servicio de Endocrinología, Hospital de Montecelo, Pontevedra, Spain

<sup>9</sup> Servicio Galego de Saúde, Santiago de Compostela, A Coruña, Spain

<sup>10</sup> Servicio Galego de Saúde, Medicina Interna, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Spain

<sup>11</sup> Servicio Galego de Saúde, Medicina Interna, Complejo Hospitalario de Santiago, Santiago de Compostela, A Coruña, Spain

<sup>12</sup> Servicio Galego de Saúde, Centro de Atención Primaria de Marín, Marín, Pontevedra, Spain

<sup>13</sup> Servicio Galego de Saúde, Servicio de Medicina Interna, Hospital da Costa, Burela, Lugo, Spain

<sup>14</sup> Servicio Galego de Saúde, Centro de Atención Primaria Cervo, Cervo, Lugo, Spain

<sup>15</sup> Servicio Galego de Saúde, Medicina Interna, Hospital da Costa, Burela, Lugo, Spain

<sup>16</sup> Servicio Galego de Saúde, Neuroloxía, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

<sup>17</sup> Servicio Galego de Saúde, Cardiología, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

## **Abstract**

*Aims.* There is little information on the familial nature of dyslipidemias in the Spanish population. This knowledge could have potential diagnostic and treatment implications. The objective of the GALIPEMIAS study was to determine the prevalence of familial dyslipidemia in Galicia, as well as determine the degree of lipid control in the participants. Prevalence of atherosclerotic cardiovascular disease (ASCVD) was also estimated. This paper presents the design, methodology and selected preliminary results.

*Methodology.* A cross-sectional study was performed in the population aged  $\geq 18$  years using cluster sampling and then random sampling. A sample of 1000 subjects was calculated and divided into three sequential phases with a specific methodology for each one. Phase I: selection of subjects from the general population and collection of informed consent documents; Phase II: collection of data from the digital clinical history to select subjects with dyslipidemia according to study criteria; Phase III: personal interview, blood analysis, family tree, and definitive diagnosis of dyslipidemia. Prevalence of different diseases and active medication was analysed. Corrected prevalence (to the reference population) of different risk factors and ASCVD was estimated.

*Results.* Phase I participation was 89.5%. We extracted complete information from 93% of the participants (Phase II). According to the study's own criteria, 56.5% ( $n = 527$ ) of the participants had some form of dyslipidemia and almost 33.7% of them had familial dyslipidemia with autosomal dominant inherit pattern. The corrected prevalence of ASCVD was 5.1% (95% CI 3.1-7.2).

*Conclusions.* Dyslipidemia was the most prevalent cardiovascular risk factor in our population with an autosomal dominant inheritance pattern in one out of every three dyslipidemia cases. Approximately, 5.1% of the sample population aged  $\geq 18$  has suffered an episode of ACVD.

## **What's known**

Cardiovascular diseases are an important health problem. Many of them are because of atherosclerosis and its complications and are grouped under the name of atherosclerotic cardiovascular diseases (ASCVD).

More than half of the adult Spanish population has dyslipidemia and an unknown proportion of these cases are because of inherited disorders. The natural history of the dyslipidemia is linked to the development of ASCVD. The proportion of patients with ASCVD and with familial dyslipidemia is unknown.

## **What's new**

We present, in detail, the methodology used on the GALIPEMIAS study (prevalence of familial dyslipidemia in an area of northwest Spain) with a sample of 1003 participants, describe the current cardiovascular situation and analyse the prevalence of ASCVD and familial dyslipidemias.

## 1 INTRODUCTION

In Spain, cardiovascular diseases are the leading cause of hospitalisation and death, cause high costs in health services<sup>1,2</sup> and rank third as a cause of disability.<sup>3</sup> Many cardiovascular diseases are because of the development of atherosclerosis and its complications and can be grouped under the atherosclerotic cardiovascular diseases (ASCVD) because they can coexist in the same patient,<sup>4</sup> share similar cardiovascular risk factors (diabetes mellitus, hypertension, smoking and dyslipidemia) and receive similar medical treatment regardless of the vascular territory involved.<sup>5</sup> Under this heading, almost all cases of coronary heart disease (CHD) or peripheral arterial disease (PAD) and many types of strokes (CeVD) are included. However, no studies have evaluated the prevalence of ASCVD in our country.

With the term “dyslipidemia”, we mean quantitative alterations of plasma lipids that include increase in total cholesterol (TC >200 mg/dL), cholesterol linked to low-density lipoprotein (LDL-C > 130 mg/dL), triglycerides (TG; >150 mg/dL) or decrease in cholesterol linked to high-density lipoprotein (LDH-C < 40 mg/dL in men or LDH-C < 50 mg/dL in women). Under this approach, more than half of the Spanish not institutionalised adult population has dyslipidemia.<sup>6,7</sup> An unknown proportion of these cases are because of inherited disorders or familial dyslipidemia, part of which are familial dyslipidemia with an autosomal dominant inheritance pattern (FDAD) as familial hypercholesterolaemia (FH), familial combined hyperlipidaemia (FCH) or familial hypertriglyceridaemia (FHTG). The natural history of these familial dyslipidemias with FDAD is linked to the development of ASCVD<sup>8,9</sup> and even premature CHD.<sup>10</sup> However, the proportion of patients with ASCVD who have some form of familial dyslipidemia with FDAD is unknown.

We designed the population-based GALIPEMIAS study (prevalence of family dyslipidemia in Galicia) to answer these questions in our community. We present, in detail, the methodology and analysis used to determine the prevalence of ASCVD and familial dyslipidemias with autosomal dominant inheritance pattern.

## 2 METHODS

A cross-sectional study was carried on a population living in the autonomous community of Galicia (northwest Spain) with an age greater than or equal to 18 years and with a health card (with provision of health services supported by the public health administration). The public health administration in Galicia promoted the study.

Sampling was performed by clusters. All the first-level clusters (health district) were represented and were assigned a sample size proportional to cluster size. Estimating a joint prevalence of FH, FCH and FHTG of 3.5% with a confidence interval of 95% and considering a design effect of 1.7% because of the type of sampling, a sample of 1000 participants was calculated.

Selection of sample: 70 municipalities of the eight community health areas were selected (by feasibility criteria). A minimum set of personal data (sociodemographic variables and telephone numbers) was acquired from the public health administration in Galicia (1.4 million people representing 61.3% of the Galician population). Over 99% of the population living in these municipalities had health cards. From this database, participants and adequate substitutes to replace mistakes and nonparticipation were selected randomly and proportionally to size of the area.

Field work was done in three successive phases to optimise data collection. The detailed methodology of each phase is explained in Table 1. In general, Phase I (telephone survey) was used to recruit participants and obtain informed consent; patients with dyslipidemia were identified in Phase II (through digital clinical history); and Phase III (physical examination) was used to characterise familial dyslipidemia with FDAD (through family trees).

**Table 1.** Methodology used in each phase

	Phase I	Phase II	Phase III
Goals	<ul style="list-style-type: none"> <li>Recruit study subjects.</li> <li>Explain the phases, the study objectives and a possible personal interview.</li> <li>Obtaining oral informed consent to access to DCH and record it.</li> <li>Collect oral health information from the participant</li> </ul>	Collect useful health information to filter subjects with possible or safe dyslipidemia under the study criteria	<ul style="list-style-type: none"> <li>Collect documentary evidence.</li> <li>Diagnose the dyslipidemia</li> </ul>
Procedures	Phone calls <sup>a</sup>	Individual review of the DCH	<ul style="list-style-type: none"> <li>Citation via phone call<sup>a</sup> and/or letter.</li> <li>Physical examination, personal interview, family tree (first degree relatives: father, mother, brothers/sisters, sons/daughters) and a blood analysis</li> </ul>
Source(s) of information	Participant	IANUS (online platform of DCH)	Participant with possible or safe dyslipidemia. IANUS (evaluation of relatives)
Who collects the data?	Trained staff (nonclinical)	13 researchers <sup>b</sup>	13 researchers <sup>b</sup>
Inclusion/exclusion criteria	<p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>Inability to collaborate (death, neurodegenerative diseases, admitted to geriatric hospitals, embarked, residents in another autonomous community).</li> <li>Oral manifestation of not wishing to participate</li> </ul>	Inclusion criteria: All subjects with oral consent in Phase I	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>All subjects that in Phase II meet one or more of the following criteria: any blood analysis (old/current) with TC <math>\geq 240</math> mg/dL or TG <math>\geq 150</math> mg/dL or LDL-C <math>\geq 160</math> mg/dL or HDL-C <math>&lt; 50</math> mg/dL (women)/<math>&lt; 40</math> mg/dL (men).</li> <li>Intake of lipid-lowering drugs recorded in DCH</li> </ul>
What information is collected?	<ul style="list-style-type: none"> <li>Oral informed consent recorded.</li> <li>Information provided by the participant (smoking habits, history of disease and current drug intake)</li> </ul>	<ul style="list-style-type: none"> <li>From the DCH (history of disease, cardiovascular risk factors, drug intake, presence of different conditions according to one or more previous blood analysis, the latest analytical data<sup>c</sup>)</li> <li>Compliance/failure criteria for Phase III</li> </ul>	<ul style="list-style-type: none"> <li>Documented information of each participant: exploration (anthropometric data, xanthomas and corneal arcus) and interview (drugs, family history, family tree), blood analysis.<sup>d</sup></li> <li>FH criteria (US Med-Ped) and <sup>39</sup> and the FCH (ISCIIE<sup>e</sup>) and <sup>40</sup></li> <li>Diagnosis of dyslipidemia</li> </ul>

DCH: Digital clinical history.

<sup>a</sup> Three or more phone calls on different days and time slots.

<sup>b</sup> Researchers: medical specialists in internal medicine (n = 7), family medicine (n = 4) and endocrinology (n = 2).

<sup>c</sup> Phase II—the latest analytical data: fasting glycaemia (mg/dL), glomerular filtration rate (GFR) (mL/min), uric acid (mg/dL), total cholesterol (TC) (mg/dL), triglycerides (TG) (mg/dL), low-density lipoprotein (LDL-C) (mg/dL), high-density lipoprotein (HDL-C) (mg/dL), creatinine (mg/dL).

<sup>d</sup> Phase III—blood analysis: haemoglobin (g/dL), leucocytes ( $\times 10^9/L$ ), platelets ( $\times 10^9/L$ ), glucose (mg/dL), urea (mg/dL), creatinine (mg/dL), uric acid, creatinine phosphokinase (CPK) (UI/L), thyroid-stimulating hormone (TSH) ( $\mu\text{UI/mL}$ ), haemoglobin A<sub>1c</sub> (%), albumin urine (micro: 20-300/macro:  $>300$ ), albumin/creatinine ratio, TC, HDL-C, LDL-C, TG, GPT/ALT (UI/L), GGT (mg/dL), GOT/AST (mg/dL), apolipoprotein A (mg/dL), apolipoprotein B (mg/dL), Anti-Nuclear Antibodies (AAN) (negative/positive titre), protein electrophoresis-serum (normal/monoclonal peak).

<sup>e</sup> Instituto de Salud Carlos III.

Two training sessions supported by printed material to homogenise the data collection criteria were performed before Phases II and III, where all 13 researchers participated.

The most recent available blood analysis within the last year was used for Phase II. If not available, a blood sample was drawn.

A family tree of the participant that included all first degree relatives (parents, siblings and children) was constructed for the diagnosis of familial dyslipidemia (Phase III). Sources of data were the patients themselves and the medical records of their relatives and information on cardiovascular events. A lipid profile was obtained.

Every single diagnosis was subsequently reviewed by a panel composed by the head researcher and at least five of the coresearchers. There were seven of these sessions during Phase III where agreement between the diagnosis of the coresearcher and the panel was assessed and a final decision was determined. The panel had full access to the digital clinical records during this process. All sessions were held in the central building of the public health administration in Galicia.

All the reported cases of ASCVD in this paper were confirmed by two experts (one neurologist and one cardiologist).

The whole process described lasted from December 2012 to January 2015.

## 2.1 Definitions

*Hypertension*<sup>11</sup>: Referred only to diagnosed and treated by reviewing the clinical digital history (CDH).

*Type 2 Diabetes mellitus*<sup>12</sup>: Documented serum fasting glucose  $\geq 126$  mg/dL (7.0 mmol/L) on two separate tests or glycosylated haemoglobin (HbA1c)  $\geq 6.5\%$  or on treatment with antidiabetic drugs.

*Dyslipidemia*: All participants that meet one or more of the following criteria: Any blood analysis (old/current) with TC  $\geq 240$  mg/dL or total TG  $\geq 150$  mg/dL or LDL-C  $\geq 160$  mg/dL or high-density lipoprotein cholesterol (HDL-C)  $< 50$  mg/dL (women) and  $< 40$  mg/dL (men).

*Atherosclerotic cerebrovascular disease (CeVD)*: the following two conditions were required in the absence of atrial fibrillation:

- Symptoms compatible as defined by the MONICA project (monitoring trends and determinants in cardiovascular disease)<sup>13</sup>: alteration of brain function with focal (or global) signs lasting more than 24 h without other apparent vascular cause.
- Image of stroke (computed tomography [CT] or magnetic resonance imaging [MRI]) or image of carotid-vertebral atheromatosis with/without significant stenosis (Doppler ultrasound, CT angiography).

*Transient ischaemic stroke*: focal neurological signs or symptoms with full recovery in less than 24 h and image of carotid-vertebral atherosclerotic with/without significant stenosis (Doppler ultrasound, CT angiography).

*Coronary heart disease: presence of any of the following:*

- Acute coronary syndrome without ST-segment elevation (NSTEMI) unstable angina or non-Q AMI.<sup>14</sup>
- Acute coronary syndrome with ST-segment elevation (STEMI)<sup>15</sup>

*Peripheral artery disease (PAD): presence of any of the following:*

- Surgery or angioplasty of the lower extremities.
- If angiography showed at least a stenotic lesion greater than 50% and/or aneurysm.
- If the index ankle/brachial pressure was less than 0.9 with typical symptoms.

*Chronic kidney disease (CKD)<sup>16</sup>: presence of kidney damage or decreased glomerular filtration rate below 60 mL/min/1.73 m<sup>2</sup> for 3 or more months, regardless of the cause that produces it.*

*Atherosclerotic cardiovascular disease: personal history of at least one of the following three criteria:*

- Atherosclerotic cerebrovascular disease
- Transient ischaemic stroke
- Peripheral arterial disease
- Coronary heart disease

*Familial dyslipidemia with autosomal dominant inheritance pattern (FDAD)<sup>17</sup>: At least 50% of first degree relatives subjects meet criteria of dyslipidemia.*

## **2.2 Statistical analysis**

Descriptive statistical analysis was performed. Qualitative variables were expressed as percentages and confidence intervals of 95%. The chi-squared test was used with the Yates' correction for continuity for the comparison between groups in qualitative variables. *P*-values of <0.05 were regarded as statistically significant. An adjustment of rates was made with the direct method to estimate the prevalence of different conditions by sex, using the population of reference (Galicia) of the year 2012 as the standard population stratified in six age groups (18-29, 30-39, 40-49, 50-59, 60-69, ≥70 years). This adjustment was done to correct the sample imbalance found in the group of women. The major diversions with regard to the population appear in the group of medium age (30-39 years [+4.8%], 40-49 years [+3.2%] and 50-49 years [+2.9%]) and in the group of elders (70-79 years [-3.4%] and ≥80 years [-4.9%]).

Statistical analysis was performed with the programmes *epidat* v.4.2<sup>18</sup> and *spss*<sup>®</sup> v.18 (SPSS Inc.; Chicago, IL, USA).

## **2.3 Ethics**

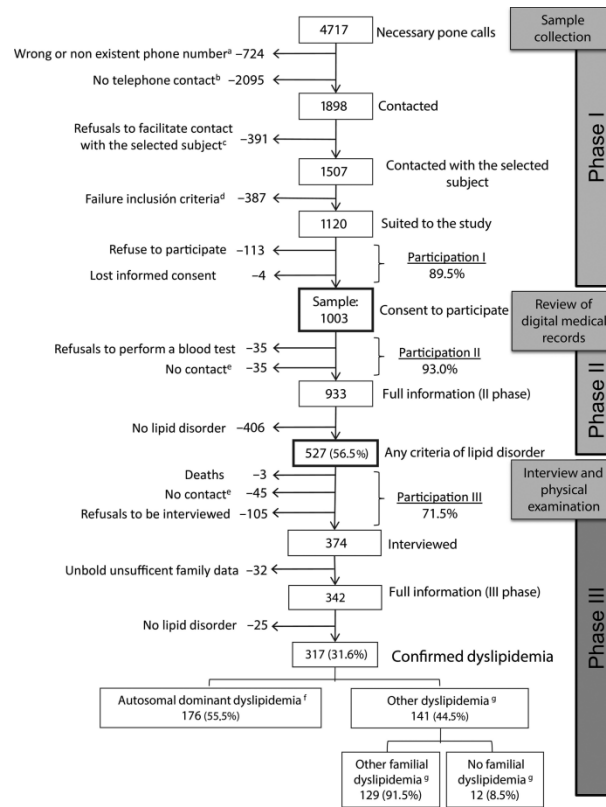
This study was approved by the Clinical Research Ethics Committee of Galicia.

Access to the medical records of the participants and their relatives through the DCH was expressly authorised (and saved as a voice record) by those participants for their best care. In addition, there was an electronic record of the reason for access to clinical information.

Newly diagnosed cases of dyslipidemia were reported and referred to their primary care physician, including information on the implications for the family when corresponding.

### 3 RESULTS

A detailed flow chart with participation rates is shown in Figure 1. The participation rate in Phase I (89.5%) refer to those selected of whom contact was made and that meet the inclusion criteria. Information was completed by 93% of participants in Phase II (n = 933). Of these, 56.5% (n = 527) of the participants had dyslipidemia and met any of the criteria established by the GALIPEMIAS study to further evaluate their lipid alteration in the next phase. In Phase III, the researchers personally contacted each participant by telephone and/or letter to solicit a personal interview and physical examination. Participation rate in this phase was 71.5%, achieving 374 interviews. The lipid profile could not be evaluated because of insufficient familial data in only 32 cases, so that in 342 cases (91.4%), full information was obtained. It was determined that there was no dyslipidemia in 25 cases and in another 12 cases there was not familial dyslipidemia (75% were related to obesity and 25% were other factors such as pregnancy, diabetes or alcoholism). Finally, a prevalence of familial dyslipidemia was observed in 30.4% of the population. Of these, a percentage of 58.0% (CI 95% = 52.5-63.9) was familial dyslipidemia with autosomal dominant inherit patterns.



**Figure 1** Flow chart of participants. <sup>a</sup>Wrong or nonexistent phone numbers: numbers of other subjects, fax numbers, nonexistent numbers. <sup>b</sup>No telephone contact after three phone calls on different days and time slots. <sup>c</sup>Refusals to facilitate contact with the selected subject: families or couples who refuse to facilitate contact with the selected subject. <sup>d</sup>Failure inclusion criteria: deaths, neurodegenerative diseases, living in geriatric hospitals, embarked, living in another autonomous community. <sup>e</sup>No contact (II and III phase) after two or more phone calls and an ordinary letter. Familial dyslipidemia: <sup>f</sup>autosomal dominant dyslipidemia; combined familial hyperlipidemia; familial autosomal dominant hypercholesterolemia; familial hipercolesterolaemia with Med-Ped score  $\geq 8$ ; familial hypertriglyceridemia (IV)). <sup>g</sup>Other dyslipidemia (other familial dyslipidemia; no familial dyslipidemia)

Table 2 shows certain characteristics of the studied sample as descriptive results obtained from the review of clinical digital history (personal history of disease, cardiovascular drugs and antidiabetic drugs). Distribution and comparison are detailed by gender.

**Table 2.** Personal history of disease and current cardiovascular and antidiabetic drug intake

	Total (n = 1003)	Men (n = 461)	Women (n = 542)	P-value
Age (M ± SD)	46.7 ± 15.0	46.1 ± 15.3	45.4 ± 15.7	0.48
Personal history of disease (collected from HCD in Phase II)				
Hypertension	18.2 (15.8-20.7)	18.7 (15.0-22.3)	17.9 (14.6-21.2)	0.76
Smoking habit	10.1 (8.2-12.0)	13.7 (10.4-16.9)	7.0 (4.8-9.3)	<b>&lt;0.001</b>
Aortic aneurysm	0.1 (0.003-0.6)	—	0,2 (0.005-1.0)	—
CKD	1.1 (0.4-1.8)	1.7 (0.4-3.0)	0.6 (1.1-1.6)	0.07
PAD	0.9 (0.3-1.5)	1.7 (0.4-3.0)	0,2 (0.005-1.0)	<b>0.02</b>
Coronary heart disease	2.0 (1.1-2.9)	3.3 (1.5-5.0)	0.9 (0.3-2.1)	<b>0.02</b>
Atherosclerotic cerebrovascular disease	0.8 (0.2-1.4)	1.3 (0.2-2.4)	0.4 (0.5-1.3)	0.2
Cardiovascular and antidiabetic drugs				
Lipid-lowering drugs	3.9 (2.8-5.3)	5.9 (3.9-8.4)	2.2 (1.1-3.8)	<b>0.003</b>
Statins	14.7 (12.6-17.1)	16.0 (12.8-19.7)	13.7 (10.9-16.8)	0.33
Antidiabetic drugs (oral and insulin)	4.9 (3.6-6.4)	7.2 (5.0-9.9)	4.8 (3.2-6.9)	0.11
Insulin	1.4 (0.8-2.3)	2.2 (1.1-4.0)	0.7 (0.2-1.9)	0.05
Anti-platelet	6.0 (4.6-7.6)	8.2 (5.9-11.1)	4.1 (2.6-6.1)	<b>0.005</b>
ACEIs and AIIRA II	14.0 (11.9-16.3)	14.8 (11.6-18.3)	13.3 (10.5-16.4)	0.5
Anti-coagulants (Sintrom®)	1.1 (0.6-1.9)	1.5 (0.6-3.1)	0.7 (0.2-1.9)	0.24
Beta-blockers	3.2 (2.2-4.5)	4.1 (2.5-6.4)	2.4 (0.1-1.6)	0.12
Calcium antagonist	4.1 (3.0-5.5)	5.5 (3.6-8.0)	3.0 (1.7-4.8)	<b>0.049</b>
Diuretics	5.0 (3.7-6.6)	4.6 (2.9-7.0)	5.4 (3.6-7.6)	0.56

ACEIs: angiotensin-converting enzyme inhibitors; AIIRA: Angiotensin receptor antagonist; CKD, chronic kidney disease; PAD: peripheral arterial disease.

Data expressed prevalence (95% confidence interval) except age.

P-value (statistical significance 0.05) of men versus women. In bold:  $p$ -value<0.05

Weight and height were measured in the subjects participating in phase III and their body mass index (BMI) was calculated. For all subjects, the mean and SD BMI was  $28.11 \pm 4.38$ , in women was  $27.8 \pm 5.04$  and in men was  $28.41 \pm 3.56$ .

Table 3 shows the crude and adjusted prevalences of the different conditions detected in any blood analysis (data from DCH). It highlights that 9.2% of participants had diabetes and the incidence was higher in men compared with women ( $P < 0.005$ ). Over 20% had at least two fasting blood tests with impaired fasting glucose ( $\geq 100$  mg/dL). About altered GFR, the 9.9% of subjects had at least one analytical test altered ( $< 60$  mL/min), and 16.2% of subjects had at least one blood analysis with uric acid  $\geq 7$  mg/dL, which was significantly higher among men (23.6%).



**Table 3.** Prevalence of selected conditions by gender

	Total (n = 933)			Men (n = 413)			Women (n = 520)			<i>P</i> -value
	CR	AR (95% CI)	N	CR	AR (95% CI)	N	CR	AR (95% CI)	N	
Diabetes	7.0	9.2 (6.8-12.3)	933	10.2	11.8 (8.2-16.5)	413	4.4	5.9 (3.3-10.2)	520	<b>0.001</b>
IFG	17.5	20.5 (17.0-24.6)	933	22.3	23.5 (18.6-29.5)	413	13.7	17.8 (13.0-24.1)	520	<b>0.001</b>
AGFR	6.8	9.9 (7.3-13.2)	932	7.7	9.6 (6.4-14.1)	413	6.0	10.2 (6.2-15.9)	519	0.28
Hyperuricemia	13.2	16.2 (13.0-20.0)	930	21.8	23.6 (18.6-29.7)	412	6.4	9.1 (5.6-14.2)	518	<b>&lt;0.0001</b>
TC ≥200 mg/dL	60.0	60.8 (55.3-66.9)	932	61.7	59.7 (52.3-68.2)	412	58.7	62.8 (54.4-72.5)	520	0.35
TG ≥150 mg/dL	31.3	33.1 (28.9-37.9)	932	39.3	38.3 (32.3-45.3)	412	25.0	29.6 (23.6-37.1)	520	<b>&lt;0.0001</b>
TC ≥240 mg/dL	32.3	34.5 (30.2-39.4)	932	32.0	32.3 (26.7-38.0)	412	32.5	36.3 (29.9-44.2)	520	0.88
cLDL ≥160 mg/dL	25.2	27.1 (23.3-31.6)	926	28.7	29.5 (23.1-36.0)	408	22.8	24.8 (19.6-31.3)	518	0.05
cHDL <50 mg/dL ♀/40 mg/dL ♂	23.8	25.7 (21.9-30.0)	925	25.6	26.6 (21.4-32.9)	407	22.4	24.8 (19.5-31.5)	518	0.26
Any criteria of lipid disorder	56.5	58.9 (53.4-65.1)	933	63.2	62.9 (55.1-71.7)	413	51.2	56.2 (48.2-65.7)	520	<b>&lt;0.0001</b>
Familial dyslipidemia with ADIP	19.0	19.7 (16.4-23.0)	933	22.8	21.8 (17.2-26.4)	413	16.0	18.6 (13.6-23.5)	520	<b>0.009</b>

Data expressed: CR: crude rate; AR: adjusted/standardised rate to the Galician population by six age groups (18-29, 30-39, 40-49, 50-59, 60-69 ≥ 70 years old); N: sample from which data are available; *P*-value (statistical significance 0.05) of men versus women. In bold: *p*-value <0.05.

IFG: impaired fasting glucose (two blood test fasting blood glucose ≥100 mg/dL <126 mg/dL); AGFR (altered glomerular filtration rate): any blood analysis with glomerular filtration rate <60 mL/min; Hyperuricemia: any blood analysis with uric acid ≥7 mg/dL; Any criteria of lipid disorder (any blood analysis (old or current) with TC ≥240 mg/dL or TG ≥150 mg/dL or cLDL ≥160 mg/dL or cHDL <50 mg/dL (♀)/<40 mg/dL (♂)). ADIP: autosomal dominant inherit pattern.

In relation to lipid profile, 60.8% of our study population had a total cholesterol ≥200 mg/dL, with 34.5% over 240 mg/dL. Approximately 33.1% of the subjects had triglycerides ≥150 mg/dL, and 27.1% had LDL cholesterol ≥160 mg/dL and both were significantly higher among men. Approximately 26.6% of men had HDL-C levels lower than 50 mg/dL, and 24.8% of women had HDL-C levels lower than 40 mg/dL.

Patients with FDAD showed, with respect to patients with other dyslipidemias, a more unfavourable lipid profile with significantly higher mean levels of TC (214 vs 198 mg/dL), LDL-C (132 vs 124 mg/dL) and TG (148 vs 103). However, the percentage of patients treated with statin (30.7% vs 27.4%) or statins plus ezetimibe (4.5% vs 3.2%) as well as the proportion of patients with LDL-C < 100 mg/dL (20.2 vs 20.6%) according to recommendations of clinical practice guidelines<sup>19</sup> for patients with FDAD, was similar in both groups (Table 4).

**Table 4.** Degree of lipid control in subjects with dyslipidemia

	Familial dyslipidemia autosomal dominant (n = 176)		Other dyslipidemia (n = 141)		All <sup>d</sup> (n = 317)		P-value <sup>c</sup>
	N	M (SD)	N	M (SD)	N	M (SD)	
TC <sup>a</sup>	174	214.2 (40.9)	140	198.6 (40.6)	314	207.2 (41.4)	<b>0.0008</b>
TG <sup>a</sup>	174	148.0 (80.6)	138	103.3 (44.1)	312	128.2 (70.5)	<b>0.0</b>
LDL-C <sup>a</sup>	168	132.5 (35.4)	138	124.6 (33.3)	306	129.0 (34.6)	0.05
HDL-C <sup>a</sup>	171	54.2 (15.6)	138	53.9 (15.7)	309	54.1 (15.6)	0.9
	<b>N</b>	<b>% (95% CI)</b>	<b>N</b>	<b>% (95% CI)</b>	<b>N</b>	<b>% (95% CI)</b>	
LDL-C < 100 <sup>b</sup>	168	20.2 (13.9-26.6)	138	21.0 (13.9-28.2)	306	20.59 (12.8-28.3)	0.98
LDL-C < 70 <sup>b,e</sup>	7	14.3 (0.4-57.9)	9	22.2 (2.8-60.0)	16	18.8 (1.0-62.2)	0.8
Statins <sup>b</sup>	176	30.7 (23.6-37.8)	141	23.4 (16.1-30.7)	317	27.4 (19.0-35.8)	0.2
Statins & Ezetimiba <sup>b</sup>	176	4.5 (1.2-7.9)	141	1.4 (0.02-8.2)	317	3.2 (0.2-6.5)	0.2

<sup>a</sup> Data expressed : N = sample from which data are available, Mean (SD) = mean and standard deviation.

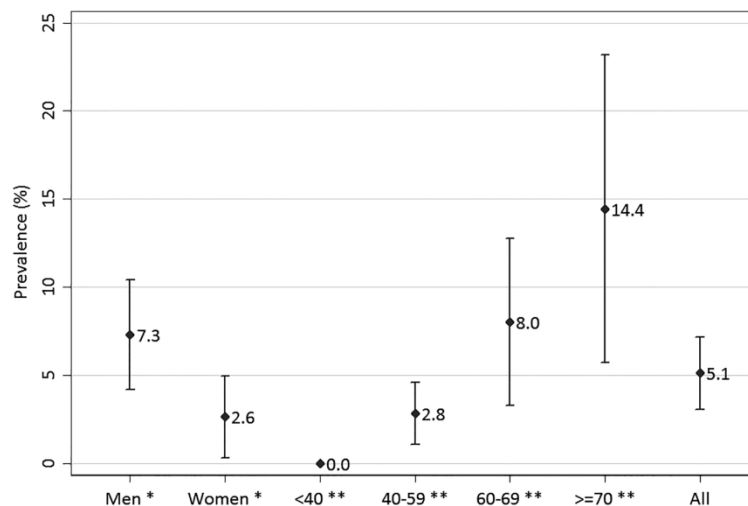
<sup>b</sup> Data expressed: N = sample from which data are available, % (95% CI) = Prevalence (95% confidence interval).

<sup>c</sup> P-value (statistical significance 0.05) of subjects with familial dyslipidemia autosomal dominant versus subjects with other familial dyslipidemia.

<sup>d</sup> All: All subjects with confirmed dyslipidemia.

<sup>e</sup> Data expressed subjects with autosomal dominant dyslipidemia and diagnosed ASCVD with LDL-C < 70 mg/dL. In bold: p-value < 0.05

Figure 2 shows the corrected prevalence of ASCVD diagnosed from the DCH. An overall corrected prevalence of 5.1 (95% CI = 3.1-7.2) was found with higher prevalence among men with 7.3% (95% CI = 4.2-10.4) than for women (prevalence of 2.6% and CI 95% = 10.3-5.0). An ascending pattern was observed with age, reaching 14.4% in subjects aged >70 (CI 95% = 5.7-23.2).



**Figure 2** Diagnosed atherosclerotic cardiovascular disease prevalences. \*Corrected prevalences by age distribution (age: <40; 40-59; 60-69; ≥70 years) in each gender in Galicia. \*\*Corrected prevalences by sex distribution in each age group in Galicia. All: Corrected prevalences by age distribution for all subjects

## 4 DISCUSSION

The present study (GALIPEMIAS) conducted on a representative sample of the Galician population (northwestern Spain) shows that dyslipidemia was present in more than half of the participants (56.5%). More importantly, in regard to health policy and previously unreported findings, one out of every three dyslipidemia cases (33.7%) show an autosomal dominant inheritance pattern. It also shows that 5.1% of the sample population  $\geq 18$  years of age have suffered an episode of ASCVD.

Prevalence of dyslipidemia in this study is similar to previous studies in Spain,<sup>6,7,20</sup> some of which did not include the Galician population.<sup>3</sup> Moreover, the prevalence of diabetes in our study (8.3%) is consistent with the results of previously published investigations,<sup>21,22</sup> as well as the diabetes study<sup>23</sup> that set in at 8%, about four points below the Spanish average. On the other hand, our investigation shows a prevalence of hypertension at 18.2%, which is lower than other investigations carried out in our country (25.5%-42.6%)<sup>24,25</sup>; however, regarding this difference, it should be noted that we only collected previously diagnosed and treated hypertension. The studies above had a prevalence of 12.9% and 26.7%, respectively. Smoking prevalence was exceptionally low in our study (10.1%) when compared with Eurobarometer data for Spain (29%)<sup>26</sup> or the 2012 Spanish National Health Survey (24%).<sup>27</sup> Several aspects can explain such a difference. First, the fact that in Galicia the proportion of smokers is lower than the Spanish average as shown by a study through the Information System of Risk Behaviour (SICRI).<sup>28</sup> Second, these studies have included people from 16 years of age and the younger age groups with a higher rate of smoking (23.8% in the 16-24 age group vs 6.4%  $\geq 65$  years) are overrepresented. Finally, although our research for smoking data was collected by standardised survey, we do not rule out that occasional smokers have self-declared as nonsmokers, which could be up to an additional 4%.<sup>29</sup>

To our knowledge, no published studies have examined the prevalence of familial dyslipidemia with an autosomal dominant inheritance pattern in the general population. Since Goldstein<sup>30</sup> reported in 1973 that 54% of the 157 hyperlipidaemic survivors of a myocardial infarction had monogenic familial dyslipidemia and its global prevalence was estimated in the same paper at 0.6-1%, there has been no research that addressed such an estimation.

In our study, the degree of lipid control in patients with FDAD was very poor. In general, only one in five patients with FDAD had a target LDL-C according to recommendations of clinical practice guidelines ( $< 100$  mg/dL). Despite these data, only 30% were being treated with statins and less than 5% were receiving combined treatment (statin plus ezetimibe). We consider a multifactorial origin for this unfavourable data that includes low level of awareness about FDAD between patients and health professionals and clinical inertia.

Finally, we found no population-based studies that have examined the prevalence of clinically relevant ASCVD by reviewing the medical records of all subjects included. Using this methodology, only limited approaches to a single vascular territory or age group detected a prevalence of 4% of acute myocardial infarction in a population over 65 years,<sup>31</sup> 7.3% rate of stroke (also embolic and haemorrhagic) in individuals  $\geq 70$  years old<sup>32</sup> or 0.78% of symptomatic PAD (ankle/brachial index of  $< 0.9$  with symptoms or revascularisation) in the population aged 35-79 years. Our partial data are consistent with those observations. In many population-based research studies, cardiovascular disease data collection (not always ASCVD) was conducted through surveys, which resulted in a greater number of biases.<sup>33,34</sup>

#### **4.1 Study limitations**

The main limitation of the study was obtaining the informed consent through telephone contact, which could have reduced the participation rate. To minimise this problem, the potential participants were informed of the affiliation of the researchers with public health administration (own service professionals, specialists in lipid disorders) as well as the personal and familial implications of a proper diagnosis.

A letter was also sent to all primary care physicians attending the selected population to keep them informed of the purpose of the study and that it was being carried out in individuals of their population (because a patient might ask about the study to his doctor).

The proportion of incorrect or nonexistent telephone numbers on the health card was very high (724 confirmed errors from 2622 successfully contacted, 27.6% of all contacts). It was impossible to estimate what proportion of the uncontacted participants was because of errors in the information of the health card, but it must be very high (deceased, second homes, changes in address, etc.). These data will be useful for further studies and researchers that require this method as it is necessary to take this into account when obtaining and calculating the sample size.

There was a deviation in the older group of women ( $\geq 70$  years) in our sample with respect to the population (Galicia). There were fewer older women in the GALIPEMIAS study. In other cross-sectional studies in which the incorporation of subjects was through telephone calls, the participation usually deviated to the opposite direction (greater number of older women), because of their availability at home. But in this case, we think that the underrepresented people correspond to the uncontacted subjects.

Another possible reason would be the exclusion criteria in Phase I, such as neurodegenerative diseases or people living in geriatric hospitals in that they could not participate in the personal interview of Phase III. This could have biased the sample in the older groups. In order to solve for this bias, a correction was made to weight the prevalence by age and gender groups.

#### **4.2 Study strengths**

One of the most important study strengths with the described methodology is the high participation obtained with the telephone calls to establish the sample and to obtain the informed consent (89.5%).

Several studies have demonstrated the validity of the DCH for epidemiological studies. This source of information allows for both a historical view of the history of illness, laboratory values and medication and lowers the economic costs in collecting epidemiological data.<sup>35-38</sup>

The selection criteria established by the study based on scientific knowledge selected susceptible subjects from the general population based on four criteria (TC  $\geq 240$  mg/dL, TG  $\geq 150$  mg/dL, LDL-C  $\geq 160$  mg/dL and HDL-C  $< 50$  [women]  $< 40$  [men]), and a comprehensive review highlighted the family tree as a tool for diagnosing familial dyslipidemia. This study was subsequently endorsed by a panel of researchers in lipids that ensured the diagnosis. Other strengths include rigorous criteria for collecting data and conducting homogenisation sessions prior to the start of the study in order to ensure that the methodology for data collection was as similar as possible between all 13 researchers.

## 5 CONCLUSION

In summary, the GALIPEMIAS study shows that dyslipidemia is the most prevalent cardiovascular risk factor in our population with an autosomal dominant inheritance pattern in one of every three dyslipidemia cases. The percentage of FDAD patients with LDL-C on target is low mostly because of the low use of statins. It also shows that 5.1% of the sample population  $\geq 18$  years of age have suffered an episode of ASCVD.

No published studies have examined the prevalence of familial dyslipidemia with autosomal dominant inheritance pattern in the general population, so the next analysis of the GALIPEMIAS data will generate greater knowledge regarding this gap.

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## CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

Conception and design: Argüeso-Armesto R, Pérez-Castro TR, Díaz-Díaz JL and Muñiz J. Acquisition of data: Argüeso-Armesto R, Díaz-Díaz JL, Rodríguez-González A, Ameneiros-Lago ME, del Alamo-Alonso AJ, de Toro-Santos JM, Fernández-Catalina PA, Pena-Seijo M, Díaz-Peromingo JA, Pose-Reino A, Názara-Otero CA, Vázquez-Freire RM, Escobar-Seoane L, Gordo-Fraile P, Castellanos-Rodríguez MM and Rodríguez-Fernández JA.

Analysis and interpretation of data: Argüeso-Armesto R, Pérez-Castro TR, Díaz-Díaz JL and Muñiz J. Drafting the manuscript: Argüeso-Armesto R, Pérez-Castro TR, Díaz-Díaz JL and Muñiz J. Revising it critically for important intellectual content: Argüeso-Armesto R, Pérez-Castro TR, Díaz-Díaz JL, Rodríguez-González A, Ameneiros-Lago ME, del Alamo-Alonso AJ, de Toro-Santos JM, Fernández-Catalina PA, Pena-Seijo M, Díaz-Peromingo JA, Pose-Reino A, Názara-Otero CA, Vázquez-Freire RM, Escobar-Seoane L, Gordo-Fraile P, Castellanos-Rodríguez MM, Rodríguez-Fernández JA, Muñiz J. Final approval of the version to be published: Argüeso-Armesto R, Pérez-Castro TR, Díaz-Díaz JL, Rodríguez-González A, Ameneiros-Lago ME, del Alamo-Alonso AJ, de Toro-Santos JM, Fernández-Catalina PA, Pena-Seijo M, Díaz-Peromingo JA, Pose-Reino A, Názara-Otero CA, Vázquez-Freire RM, Escobar-Seoane L, Gordo-Fraile P, Castellanos-Rodríguez MM, Rodríguez-Fernández JA, Muñiz J

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