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Title:

Frank´s Sign and cardiovascular risk: an observational descriptive study.

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Abstract

Purpose: To analyze the relationship between the diagonal earlobe crease (DELC) and the main indices of cardiovascular risk (CVR), considering the crease's anatomical variations.

Methods: The study group consisted of 1050 adults residing in A Estrada town (Spain). Participants underwent the following determinations: age, sex, body mass index, smoking habit, blood pressure, glycemia, glycated hemoglobin, total cholesterol, HDL-C, LDL-C, and cardiovascular events. CVR was calculated applying the Framingham-Anderson equation, the SCORE equation and the ASCVD risk calculator. Both earlobes were examined, recording DELC presence, length and depth, and presence of accessory creases. Results were analyzed by using chi-square test, Student's t-test, ANOVA, Mann-Whitney or Kruskal-Wallis tests. To extract the functions of CVR, a script in R was created (https://cran.r-project.org/).

Results: The estimated cardiovascular mortality risk was significantly higher in patients who presented DELC ($p<0.001$). According to the "European Guidelines on cardiovascular disease prevention", some 76.1% of patients who showed no DELC had low CVR, this percentage decreasing significantly as the presence of the crease increased (64.4% for unilateral and 42.1% for bilateral; $p<0.001$). The number of individuals with moderate, high or very high CVR increased significantly as the presence of the crease increased (23.8% had no crease, 35.6% had unilateral creases, and 58% had bilateral creases; $p<0.001$). The mean CVR estimated was significantly higher for patients with higher DELC length scores ($p<0.001$), with higher DELC depth scores ($p<0.001$), and with accessory creases ($p<0.001$).

Conclusions

The DELC is independently associated with higher CVR values, especially when the crease is complete, bilateral, deep and has accessory creases.

Introduction

According to the World Health Organization, cardiovascular diseases (CVDs) represent the leading cause of death worldwide, with 17.9 million deaths each year, a third of which occur prematurely in individuals younger than 70 years (1). CVDs also involve significant morbidity and loss of quality of life, to the point where the disability-adjusted life years and years of life lost of patients with CVDs have doubled in the past 30 years (2). Of special interest, therefore, are prevention programs based on promoting healthy lifestyles and controlling potentially modifiable risk factors such as tobacco use, high systolic blood pressure, diabetes, high low-density lipoprotein cholesterol and obesity (2,3).

Assuming that CVDs have a multifactorial etiology and in an attempt to jointly assess the risk factors, the calculation of the cardiovascular risk (CVR) was proposed and involves a series of mathematical functions that define the likelihood that an individual will present a cardiovascular episode, especially an acute coronary or stroke event within a specified period (4). The most widely used prediction indices for CVR are the Framingham-Anderson equation (5), the Systematic Coronary Risk Evaluation (SCORE) equation (6) and the Atherosclerotic Cardiovascular Disease Risk Score (ASCVD) (7). Although these CVR prediction indices are regularly applied in Europe and the U.S., it has been suggested that there is a need for developing specific indices for different countries and populations, because the risk assessment tools developed for one specific population often are inaccurate when applied to other populations (4). Although the ideal scenario would be the ability to estimate the CVR in all adults, this initiative depends on each country’s health policies and resources. It is therefore

important to identify the most common physical signs related to atherosclerosis and CVD, such as xanthelasmas (8), corneal arcus (9), acanthosis nigricans (10) and obesity (11).

In 1973, the United States pulmonologist Saunders T. Frank described the diagonal earlobe crease (DELC), which consists of an oblique line that travelled from the tragus to the pinna (Figure 1A, 1B), generally bilateral and clearly visible on inspection, shown by some of his patients with a history of angina pectoris, electrocardiographic ischemic changes or coronary artery disease confirmed angiographically (12). The author was therefore attributed with the initial report of an association between this physical sign, which was named after him, and coronary artery disease (13). This finding was immediately replicated in a clinical study published in 1974, in which a significant and independent statistical association was found between the presence of the DELC and coronary artery disease, with a prevalence of 47% in the cases and 30% in the controls (14).

Since then, numerous published articles have confirmed that the DELC is an independent predictor of the onset of CVD and is closely associated with an increase in its prevalence, extent and severity (15-35), In most published studies, the sensitivity of DELC as a diagnostic tool for atherosclerosis was above 75% (27), and its specificity exceeded 85% (25). Only a minority of researchers suggested that the association between the DELC and atherosclerosis is not independent and is due to both entities being related to atherogenic risk factors such as hypertension (36), tobacco use (37), obesity (38), diabetes (39) and hypercholesterolemia (40). However, the histomorphological analysis of the DELC recently performed by our group revealed a redistribution of connective tissue and poor capillary density, which allows us to speculate that the DELC could represent an early indicator of peripheral microangiopathy (41).

To date, we have found only 3 articles in the literature that studied the relationship between the DELC and the indices of CVR, without considering in any case the crease's characteristics (29,42,43). Accordingly, this study's main objective was to analyze the relationship between the DELC and the main indices of CVR, considering the crease's anatomical variations.

Material and Methods

- *Study group*

The study participants were selected within the framework of the "A Estrada Study of Glycation and Inflammation" (AEGIS), approved by the Clinical Research Ethics Committee of Galicia, Spain (CEIC2012-025). AEGIS is a populational study conducted in the northwest of Spain, in the municipality of A Estrada (Pontevedra) that, during recruitment, had 18,744 inhabitants older than 18 years.

The sample selection was stratified by the following age groups (in years): 18–29, 30–39, 40–49, 50–59, 60–69, 70–79 and older than 80. Using software, a random sample was generated of 500 individuals belonging to each age group, for a total of 3500 individuals. After excluding those who declined to participate, those who had died, those who did not respond, those who no longer lived in the municipality, those with no health coverage and those who did not meet the inclusion criteria due to presenting dementia, intellectual disability, severe cerebrovascular disease, cancer, terminal illness or inability to communicate, a study group was created with 1050 participants: 468 men (44.6%) and 582 women (55.4%), with a mean age of 52 ± 19.1 years.

- *Collection of demographic, medical and laboratory data*

Between November 2012 and March 2015, the participants attended the Health Center of A Estrada (Pontevedra) where they were evaluated by a team of previously trained and calibrated health practitioners (physician, nurse and dentist). Each participant

underwent a clinical interview and a set of specific determinations that included the following:

- Structured questionnaire with demographic and anthropometric data, recording the age and sex and calculating the body mass index (BMI). An individual was considered to not have excess weight with BMI values <25 kg/m^2, to have excess weight with BMI ≥25 kg/m^2 and <30 kg/m^2 and to have obesity with BMI ≥30 kg/m^2.

- Smoking habit recording. An individual was considered to be a smoker if they consumed ≥1 cigarette a day or had stopped smoking less than 1 year ago.

- Evaluation of mean blood pressure using an automatic WatchBP Office ABI device (Micro, Barcelona, Spain). An individual was considered to have hypertension if their systolic blood pressure was ≥140 mm Hg, if their diastolic blood pressure was ≥90 mm Hg or if they were undergoing antihypertensive drug therapy.

- Measurement of serum glucose levels using the Accu-Chek Guide Me system (Roche, Barcelona, Spain) and of glycated hemoglobin (HbA1c) using the Arkray HA 8140 analyzer (Menarini Diagnostics, Barcelona, Spain). The HbA1c values were converted from the reference JDS/JSCC system (Japanese Diabetes Society/Japanese Society for Clinical Chemistry) to the standardized DCCT/NGSP system (Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program) (4). An individual was considered to have diabetes if they were undergoing hypoglycemic therapy or had fasting blood glucose levels ≥126 mg/dL or HbA1c levels ≥6.5%.

- Measurement of serum levels of total cholesterol, HDL-C and LDL-C using standard commercial methods. An individual was considered to have hypercholesterolemia with serum cholesterol levels ≥250 mg/dL, LDL-C levels ≥130 mg/dL or if they were undergoing lipid-lowering therapy.

- Cardiovascular events. We collected the participants' history of ischemic heart disease and cerebrovascular disease. Additionally, each individual underwent a 12-lead electrocardiogram to mainly investigate the presence of a pathological Q wave.

- *Cardiovascular risk stratification*

Based on the recorded variables, we calculated the CVR applying 3 prediction indices: the Framingham-Anderson equation (5), the SCORE equation (6) and ASCVD (7).

- *Inspection of the diagonal earlobe crease*

We examined both earlobes, recording the variable "absence/presence of the DELC". We categorized the length of each crease, considering as "full length" the oblique line that extends from the tragus to the posterior edge of the pinna. We established three categories: 1, extending <1/3 of the full length; 2, extending ≥1/3 and <2/3 of the full length; and 3, extending ≥2/3 of the full length. Based on these scores, we calculated the variable "total length", the result of summing the values corresponding to the categories of the crease length for both ears. Thus, the total length achieved a score of 1 to 6.

For the depth of the DELC based on its penetration into the skin, we attributed 2 categories: 1, superficial crease; and 2, deep crease (Figure 1A, 1B). We calculated the variable "total depth", the result of summing the crease depth categories for both ears. Thus, the total depth achieved a score of 1 to 4.

We analyzed the absence/presence of secondary or accessory creases in each lobe, considering this variable to be any additional crease to the main crease.

The variables were measured by 2 trained and calibrated examiners. To check the reproducibility of the results, we repeated the measurements of 10 randomly selected cases one month after the first measurements, obtaining for all evaluated variables an intraclass correlation coefficient that varied between 0.89 and 0.99.

- *Statistical analysis*

The relationship between the 2 qualitative variables (e.g., presence/absence of accessory creases and male/female) was assessed using the chi-squared test. To study the influence of a qualitative variable (e.g., presence/absence of the DELC) on the mean values of a quantitative variable (e.g., estimated CVR), we used Student's t-test and analysis of variance (ANOVA) or the nonparametric Mann-Whitney or Kruskal-Wallis tests, in the event of non-normal distributions. Values of $p<0.05$ were considered statistically significant. To extract the functions of CVR, we created a script in R (https://cran.r-project.org/). This software was also employed in the data analysis, as well as the SPSS program for Windows version 19 (SPSS Inc, Chicago, USA).

Results

- *Description of the diagonal earlobe crease in the study population*

Of the 1050 individuals who participated in the study, the examination of both ears was completed in 1048 (2 patients could not be analyzed in one of the ears due to ablation or traumatic deformation of the lobe). The DELC was bilateral in 56.9% of the participants, unilateral in 8.3% and not detected in 34.9% of the cases. No predilection for any particular ear was observed; 59.2% of the sample presented a right ear crease and 59.3% presented a left ear crease. In 71.5% of the participants with creases, these occupied at least 2/3 of the full length in at least one ear; in 45.7%, the creases of both ears reached the maximum score. The percentage distribution of deep and superficial creases was 32.4% and 26.1% for the right ears versus 31.3% and 27.5% for the left ears, respectively. In 45.2% of the cases, the total depth of the DELC reached the maximum score, which implies the bilateral presence of a deep crease. In contrast, the most uncommon condition (9.1% of the cases) was the coexistence of a superficial crease and a deep crease in the same individual. We detected secondary creases in

68.0% and 65.4% of the right and left ears, respectively. When the DELC was bilateral, the rate of secondary creases in both ears was 62.5%.

There were no statistically significant differences between the men and women in terms of the prevalence of the DELC (p=0.167), its total length (p=0.380), its depth (p=0.735) or the presence of bilateral secondary creases (p=0.723). In general, the presence of unilateral or bilateral DELCs, their total length, their total depth and the presence of secondary creases increased significantly with age (p<0.001).

- *Description of the cardiovascular risk indices in the study population (Table 1)*

The mean cardiovascular mortality risk at 10 years was 10.6±11.5% (low/moderate risk) with a range of 0.4–70.8 when estimated with the Framingham index, 1.1±1.3% (moderate risk) with a range of 0.0–7.9 with SCORE, and 11.9±13.6% (high risk) with a range of 0.1–73.5 with ASCVD. The percentages of individuals with a “high” estimated risk when applying the various cutoff points established in the definitions of each index without considering the rest of the modifiers for the Framingham, SCORE and ASCVD indices were 16.6%, 4% and 45.9%, respectively. Applying the qualitative risk stratification established in the European cardiovascular disease prevention guidelines considering the modifiers (45,46), 21.8% of the study participants had “high” or “very high” risk, according to the SCORE index.

- *Relationship between the estimated cardiovascular risk and the diagonal earlobe crease*

The mean cardiovascular mortality risk estimated by applying the 3 indices described above was significantly higher in the patients who presented a DELC (p<0.001). For the Framingham index, the mean CVR increased from the total absence of the DELC (5.4%) to the bilateral presence of the crease (14%), a difference that reached statistical significance (p<0.001), which implies going from low risk to moderate risk. With the SCORE function, the mean CVR increased significantly from 0.6% for the

patients who showed no DELC in any of their ears to 1.4% for those who had bilateral creases ($p<0.001$), which implies going from a low risk for the patients without creases or with unilateral creases to a moderate risk in the individuals who presented creases in both ears. With the ASCVD index, we also observed a significant increase in the mean estimated risk, increasing from 5.7% in the absence of DELC to 14.2% in the presence of bilateral creases ($p<0.001$), which implies a change from the low risk to the high risk category.

Table 2 shows the relationship between the presence of the DELC and the qualitative stratification of CVR according to the indications of the European guidelines on cardiovascular disease prevention (45,46). Some 76.1% of the patients who showed no DELC in any of their ears had low CVR, while the percentage of individuals in this risk category decreased significantly as the presence of the crease increased (64.4% for unilateral and 42.1% for bilateral; $p<0.001$). The number of individuals with moderate, high or very high CVR increased significantly as the presence of the crease increased (23.8% had no crease, 35.6% had unilateral creases, and 58% had bilateral creases; $p<0.001$).

The mean CVR estimated using the 3 previously described indices was significantly higher for the patients with higher total DELC length scores ($p<0.001$) (Table 3). Applying the Framingham index, the patients with scores ≥2 (DELC extending ≥1/3 and <2/3 of the full length) went from the low to moderate category of CVR. Applying the SCORE index, the patients with total DELC length scores ≥2 were classified into the moderate risk category. Applying the ASCVD index, the patients with a score ≥2 went from the low to moderate category of CVR.

The mean CVR estimated with the 3 indices was significantly higher for the patients with higher total DELC depth scores ($p<0.001$) (Table 4). With the Framingham and SCORE indices, the patients with scores ≥2 (deep unilateral DELC) reached the

moderate CVR level; with this same score and applying the ASCVD index, the patients reached a high CVR level.

The mean CVR estimated with the 3 indices was significantly higher for the patients who presented a secondary crease ($p<0.001$). The values obtained with the SCORE index in the presence of a secondary unilateral or bilateral crease implied a moderate CVR; however, for the patients who had no secondary crease, the CVR was low. Although statistically significant differences were detected with the Framingham and ASCVD equations in the mean CVR value based on the presence of unilateral or bilateral secondary creases ($p<0.001$), these did not imply a change in the CVR category (Table 5).

Discussion

This study showed that the DELC is a common anatomical accident in adults of both sexes whose prevalence and morphological characteristics are accentuated with age. DELC is independently associated with higher values for the predictive indices of CVR.

Although the association between CVD and the DELC has generated significant controversy, most articles published to date have confirmed that the DELC is an independent predictor of CVD and atherosclerotic disease (29,42,43). Only a small number of researchers reject any correlation between the DELC and CVD, in contrast to the results of our study. The majority of the studies have significant methodological biases, such as a very small number of patients (47) and no adjustment for age (38); however, there are 2 important populational studies in which an association between the DELC and CVD could not be demonstrated, in which 1237 Japanese-American men aged 50 to 74 years (48) and 3155 Chinese patients (49) participated, respectively. It has been suggested that racial characteristics might determine the

results (50), either by the presence of genetic factors involved in its etiology (26) or by the distinct lifestyles of these populations (51).

In 1982, Pasternac and Sami (52) suggested that the integration of the DELC in the risk profile of the Framingham index could increase its predictive accuracy, in terms of the presence and severity of coronary artery disease. To date, however, we have found only 3 studies that analyzed the relationship between the earlobe crease and any of the validated indices of cardiovascular risk (29,42,43). The most substantial differences with respect to the present study is that 2 of these articles applied only the Framingham index, while the third used the Framingham and SCORE indices. None of the articles resorted to the ASCVD equation or considered the crease length, its depth or the presence of accessory creases. The first of these studies was a cross-sectional study performed by Kang et al. (42) with the objective of assessing the relationship between the DELC and metabolic syndrome. To this end, the authors recruited 3835 patients between the ages of 20 and 79 years who attended a health check-up in a primary care facility. The authors found a statistically significant relationship between the presence of the DELC and the Framingham CVR index. The prevalence of the crease was higher in the high CVR group, although the authors indicated that this result could be due to the small number of individuals included in this risk level (a history of CVD was considered an exclusion criterion).

Christoffersen et al. (29) assessed the results of the Copenhagen City Heart Study whose participants consisted of 10,885 Danish individuals who were representative of the general population; the participants underwent prospective follow-up between 1976 and 2011. The authors' initial conclusion was that certain visible signs classically related to age, such as the DELC, were associated with a greater risk of ischemic heart disease, myocardial infarction and death, regardless of chronological age and known CVR factors. To improve the CVR classification, the authors analyzed the inclusion of these signs (DELC, male pattern baldness and xanthelasma) in the predictive

Framingham risk model. Of the 922 patients included in the study with no history of myocardial infarction and with moderate CVR according to the Framingham model, 91 were reclassified to a lower risk and 30 to a higher risk when also considering the presence of these signs. The authors concluded that these signs could improve the accuracy of the CVR risk classification when implemented into the Framingham score model, especially in the moderate risk group, which classically is considered an inexact risk level. This change would help discriminate individuals of lower risk from those of high risk; the former could be treated only with lifestyle changes, while the latter would benefit from more intensive lipid-lowering therapy.

In contrast, Aligisakis et al. (43) published a prospective study that included 6733 patients, whose most outstanding result was that, despite finding a statistically significant relationship between the DELC and the recalibrated SCORE, Framingham, and recalibrated Framingham risk indices, this relationship stopped being significant for the 3 indices that predicted CVR when adjusting for age, sex and BMI.

Our study found that the CVR estimated using the 3 indices (Framingham, SCORE and ASCVD) was significantly higher for the patients who showed some DELC, obtaining higher values when the crease was bilateral. Aligisakis et al. (43) found no differences between unilateral or bilateral DELC, Kang et al. (42) did not record this variable, and Christoffersen et al. (29) assessed only the creases present in the right ear.

None of these 3 studies considered the length of the DELC, its depth or the presence of accessory creases. We cannot therefore compare our results that demonstrate a significant increase in CVR as the morphological characteristics of the crease increase.

The strengths of the present study include 1) the random selection of a population sample representative of the general adult population, without severe concomitant medical conditions, which avoids the bias of hospitalized patients, who typically present a larger number and/or severity of comorbidities (29,43); 2) the inclusion of patients of

both sexes (53,33); and 3) the sample size of 1050 participants, because very few such studies have had samples larger than 1000 individuals (30). This study is not exempt from a number of limitations that should be considered when analyzing its results and comparing them with those of previous studies, such as its cross-sectional nature and the characterization of the DELC in terms of unilaterality-bilaterality and length. A number of authors have considered that the DELC is present when it appears on at least one ear (42,54), while others acknowledge only the bilateral presentation (27, 54). Numerous authors have considered that the DELC is present when it occupies at least 2/3 of the distance between the tragus and the pinna (33, 53, 54), while others are satisfied with 1/3 of this distance (32).

In short, the DELC is a common anatomical accident among the adult population of both sexes, whose morphological characteristics are accentuated with age and is independently associated with higher CVR values calculated using contrasted predictive indices, especially when the crease is complete, bilateral, deep and has accessory creases. We can therefore confirm that the presence of this anatomical accident represents an indicator for CVR.

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Figures, Tables

Figure 1A. Superficial diagonal earlobe crease

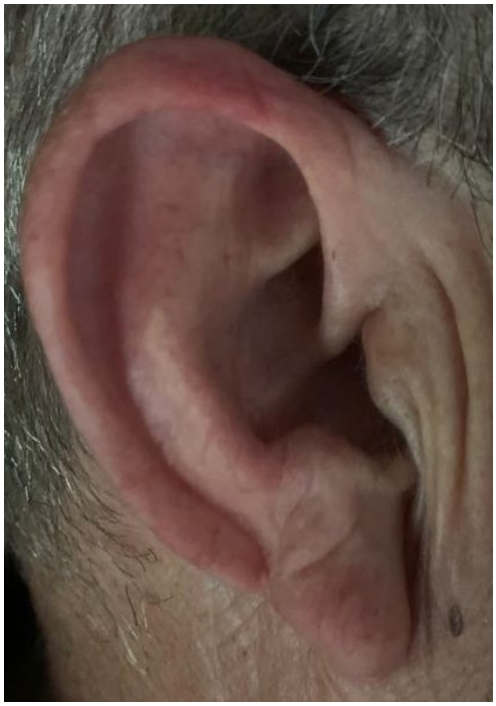

Figure 1B. Deep diagonal earlobe crease

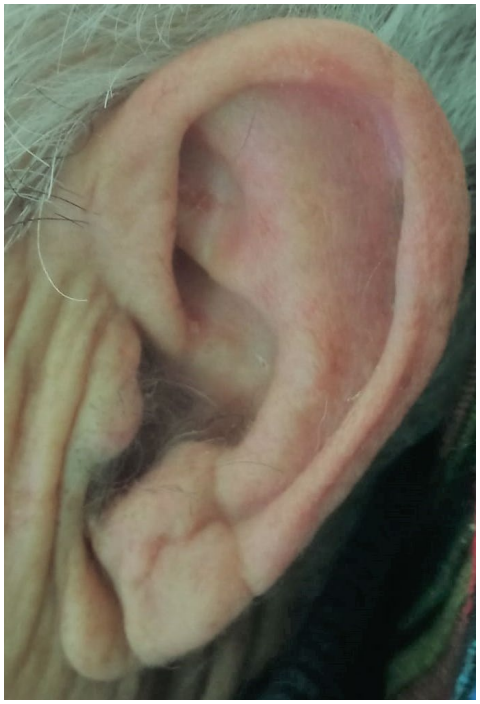

Table 1. Cardiovascular risk estimated based on the presence of the diagonal earlobe crease

ESTIMATION METHOD	PRESENCE OF THE CREASE	n	ESTIMATED CARDIOVASCULAR RISK (%)		
			Mean ± SD	Median	Range
Framingham	**0**	238	5.4 ± 8.3	2.7	0.5–62.0
	1	74	8.1 ± 9.2	4.2	0.8–42.7
	2	424	14.0 ± 12.2	10.4	0.4–70.8
	Total	736	10.6 ± 11.5	6.3	0.4–70.8
SCORE	**0**	108	0.6 ± 0.9	0.2	0.02–6.9
	1	46	0.8 ± 1.0	0.5	0.0–5.1
	2	260	1.4 ± 1.5	1	0.0–7.9
	Total	413	1.1 ± 1.3	0.7	0.0–7.9
ASCVD	**0**	121	5.7 ± 1.0	1.7	0.1–49.9
	1	55	8.3 ± 12.9	2.8	0.1–52.4
	2	431	14.2 ± 14.0	9.4	0.2–73.6
	Total	607	12.0 ± 13.7	6.5	0.1–73.6

n, number of individuals evaluated; DS, standard deviation; Framingham, Framingham-Anderson equation; SCORE, systematic coronary risk evaluation equation; ASCVD, atherosclerotic cardiovascular disease equation; 0, no crease; 1, unilateral crease; 2, bilateral crease.

Table 2. Cardiovascular risk estimated according to the categorical classification for the SCORE index, depending on the presence of the diagonal earlobe crease

ESTIMATED CARDIOVASCULAR RISK CATEGORY	Diagonal earlobe crease		
	Absent, n (%)	Unilateral, n (%)	Bilateral, n (%)
Very high (n=41)	6 (5.5)	5 (11.1)	30 (11.5)
High (n=49)	8 (7.3)	3 (6.7)	38 (14.7)
Moderate (n=102)	12 (11)	8 (17.8)	82 (31.7)
Low (n=221)	83 (76.2)	29 (64.4)	109 (42.1)

SCORE, Systematic Coronary Risk Evaluation equation; n, number of individuals; %, percentage of individuals.

Table 3. Cardiovascular risk estimated based on the length of the diagonal earlobe crease

ESTIMATION METHOD	CREASE LENGTH	n	ESTIMATED CARDIOVASCULAR RISK (%)		
			Mean ± deviation	Median	Range
Framingham	**1**	44	5.4 ± 5.9	3.0	0.8–34.1
	2	71	10.2 ± 10.5	7.2	0.5–57.8
	3	52	10.1 ± 10.5	5.9	0.6–42.7
	4	79	13.7 ± 11.8	9.6	1.0–57.9
	5	49	14.7 ± 12.1	11.4	2.7–70.9
	6	195	16.4 ± 12.8	12.9	1.0–69.9
	Total	735	10.6 ± 11.5	6.5	0.5–70.9
SCORE	**1**	21	0.5 ± 0.5	0.3	0.0–2.0
	2	47	1.2 ± 1.3	0.8	0.0–5.2
	3	33	1.4 ± 1.7	0.8	0.1–8.0
	4	57	1.4 ± 1.3	1.0	0.0–6.9
	5	33	1.7 ± 1.5	1.5	0.1–6.2
	6	110	1.5 ± 1.5	1.0	0.0–7.7
	Total	413	1.2 ± 1.4	0.7	0.0–8.0
ASCVD	**1**	24	4.8 ± 8.2	2.5	0.1–40.4
	2	58	8.6 ± 9.9	5.0	0.3–41.4
	3	40	10.8 ± 14.1	4.6	0.6–52.4
	4	74	10.2 ± 10.7	6.1	0.2–49.0
	5	52	12.8 ± 11.0	9.9	0.8–54.8
	6	232	17.4 ± 15.5	13.4	0.2–73.6
	Total	606	11.9 ± 13.6	7.6	0.1–73.6

n, number of individuals evaluated; Framingham, Framingham-Anderson equation; SCORE, Systematic Coronary Risk Evaluation equation; ASCVD, Atherosclerotic cardiovascular disease Risk equation; 1, 2, 3, 4, 5 and 6: the sum of the values of the length of the crease in both ears (values for each crease: 1, extending <1/3 of the full length; 2, extending ≥1/3 and <2/3 of the full length; 3, extending ≥2/3 of the full length).

Table 4. Cardiovascular risk estimated based on the depth of the diagonal earlobe crease

ESTIMATION METHOD	DEPTH OF THE CREASE	n	ESTIMATED CARDIOVASCULAR RISK (%)		
			Mean ± deviation	Median	Range
Framingham	**0**	213	5.4 ± 8.6	2.6	0.5–62.0
	1	56	7.0 ± 8.1	3.7	0.8–42.7
	2	157	10.8 ± 11.1	7.1	0.5–55.1
	3	37	12.0 ± 9.7	9.8	1.1–41.5
	4	155	16.1 ± 12.0	13.7	1.0–70.9
	Total	617	10.0 ± 11.0	7.1	0.5–70.9
SCORE	**0**	99	0.6 ± 1.1	0.3	0.0–7.4
	1	30	0.8 ± 1.0	0.5	0.0–5.2
	2	102	1.0 ± 1.1	0.7	0.0–7.7
	3	24	1.4 ± 1.2	1.0	0.1–4.6
	4	93	1.8 ± 1.7	1.3	0.0–8.0
	Total	349	1.1 ± 1.4	0.75	0.0–8.0
ASCVD	**0**	110	5.6 ± 9.7	1.7	0.1–49.9
	1	35	6.3 ± 9.1	3.3	0.4–43.2
	2	139	10.5 ± 13.1	4.8	0.1–73.6
	3	36	11.4 ± 11.4	6.9	0.9–51.3
	4	184	17.2 ± 14.7	13.4	0.3–68.8
	Total	504	11.6 ± 13.5	7.3	0.1–73.6

n, number of individuals evaluated; Framingham, Framingham-Anderson equation; SCORE, Systematic Coronary Risk Evaluation equation; ASCVD, Atherosclerotic cardiovascular disease Risk equation; 0, 1, 2, 3 and 4: the sum of the values of the depth of the crease in both ears (values for each crease: 0, no crease; 1, superficial crease; 2, deep crease).

Table 5. Cardiovascular risk estimated depending on the presence of secondary creases of the diagonal earlobe crease

ESTIMATION METHOD	PRESENCE OF SECONDARY CREASES	n	ESTIMATED CARDIOVASCULAR RISK (%)		
			Mean ± deviation	Median	Range
Framingham	**0**	425	6.9 ± 9.2	3.6	0.5–62.0
	1	65	14.4 ± 11.5	10.8	1.9–57.9
	2	245	16.0 ± 12.6	12.8	1.3–70.9
	Total	736	10.6 ± 11.5	7.3	0.5–70.9
REGICOR	**0**	343	2.2 ± 2.3	1.5	0.1–16.4
	1	64	3.7 ± 2.8	2.6	0.6–14.7
	2	239	3.8 ± 3.0	3.0	0.4–20.0
	Total	645	3.0 ± 2.8	2.2	0.1–20.0
SCORE	**0**	226	0.4 ± 11.9	0.4	0.0–7.7
	1	43	1.6 ± 1.7	0.9	0.1–8.0
	2	145	1.6 ± 1.4	1.3	0.0–7.0
	Total	413	1.2 ± 1.4	0.8	0.0–8.0
ASCVD	**0**	267	7.3 ± 10.9	2.7	0.1–52.4
	1	65	12.6 ± 12.8	8.5	0.5–57.6
	2	275	16.4 ± 14.8	12.0	0.3–73.6
	Total	607	12.0 ± 13.7	7.5	0.1–73.6

n, number of individuals evaluated; Framingham, Framingham-Anderson equation; SCORE, systematic coronary risk evaluation equation; ASCVD, atherosclerotic cardiovascular disease equation; 0, no secondary creases; 1, secondary creases present in one ear; 2, secondary creases present in both ears.