Rev Esp Cardiol. 2012;**65(8)**:726–733

Original article

# Prevalence and Clinical Characteristics of Peripheral Arterial Disease in the Study Population Hermex

Francisco J. Félix-Redondo,[a,*] Daniel Fernández-Bergés,[b] María Grau,[c] José M. Baena-Diez,[d] José M. Mostaza,[e] and Joan Vila[c]

[a] *Centro de Salud Villanueva Norte, Servicio Extremeño de Salud, Villanueva de la Serena, Badajoz, Spain*
[b] *Unidad de Investigación Área de Salud, Programa de Enfermedades Cardiovasculares, Servicio Extremeño de Salud y Fundesalud, Villanueva de la Serena, Badajoz, Spain*
[c] *Grupo de Epidemiología y Genética Cardiovascular, Programa de Investigación en Procesos Inflamatorios y Cardiovasculares, IMIM, Barcelona, Spain*
[d] *Centro de Salud La Marina, Instituto de Investigación en Atención Primaria Jordi Gol, Institut Català de la Salut e IMIM, Barcelona, Spain*
[e] *Unidad de Arteriosclerosis, Hospital Carlos III, Madrid, Spain*

*Article history:*
Received 15 October 2011
Accepted 5 March 2012
Available online 23 June 2012

*Keywords:*
Peripheral arterial disease
Intermittent claudication
Ankle brachial index
Epidemiology
Risk factor
Cardiovascular disease
Alcohol consumption
Physical activity

ABSTRACT

*Introduction and objectives:* To estimate the prevalence of peripheral arterial disease as measured on ankle-brachial index and evaluate the associated risk, clinical, and diagnostic factors.

*Methods:* Cross-sectional study conducted in a random population-based sample of 2833 individuals aged 25 to 79 years from Don Benito health area (Badajoz). Peripheral arterial disease was considered for ankle-brachial index<0.90. To identify symptomatic disease we used the Edinburgh questionnaire. The current screening recommendations, changes to other categories of estimated coronary risk associated with index measurements, and the association with risk factors were assessed.

*Results:* The prevalence of peripheral arterial disease was 3.7% (95% confidence interval, 3.0%-4.5%), 5.0% (3.9%-6.3%) in men and 2.6% (1.8%-3.5%) in women (*P*=.001). The cumulative prevalence in those aged 50, 60 and 70 years were 6.2%, 9.1%, and 13.1% respectively. The disease was symptomatic in 13.3% (6.8%-19.8%) of cases and 29.6% of asymptomatic patients were not detected as recommended for high-risk groups. The use of ankle-brachial index increased the number of individuals with high coronary risk by 32.7%. Peripheral arterial disease was positively associated with age, smoking, hypercholesterolemia, sedentary lifestyle, microalbuminuria and history of cardiovascular disease, and negatively with alcohol consumption.

*Conclusions:* The use of ankle-brachial index for peripheral arterial disease diagnosis is advisable because of the low prevalence of symptomatic cases and the associated change in estimated coronary risk. Screening groups should be adapted to the Spanish population. Smoking and hypercholesterolemia are major associated risk factors.



## Prevalencia y características clínicas de la enfermedad arterial periférica en la población general del estudio Hermex

*Palabras clave:*
Enfermedad arterial periférica
Claudicación intermitente
Índice tobillo-brazo
Epidemiología
Factor de riesgo
Enfermedad cardiovascular
Consumo de alcohol
Actividad física

RESUMEN

*Introducción y objetivos:* Determinar la prevalencia de enfermedad arterial periférica mediante el índice tobillo-brazo y evaluar los factores de riesgo, clínicos y diagnósticos asociados.

*Métodos:* Estudio transversal realizado entre 2007 y 2009, con muestra aleatoria de 2.833 sujetos entre 25 y 79 años representativa del área de salud de Don Benito (Badajoz). Se consideró diagnóstico de enfermedad arterial periférica un índice tobillo-brazo < 0,90. Se utilizó el cuestionario de Edimburgo para identificar formas sintomáticas. Se evaluaron las recomendaciones actuales de cribado, los cambios del riesgo coronario estimado conseguidos con su uso y la asociación con los factores de riesgo.

*Resultados:* La prevalencia de enfermedad arterial periférica fue del 3,7% (intervalo de confianza del 95%, 3,0-4,5%); el 5,0% (3,9-6,3%) en varones y el 2,6% (1,8-3,5%) en mujeres (p = 0,001). Las prevalencias acumuladas a partir de 50, 60 y 70 años fueron del 6,2, el 9,1 y el 13,1% respectivamente. La enfermedad era sintomática en el 13,3% (6,8-19,8%) de los casos. Las recomendaciones actuales de cribado no detectaron al 29,6% de los enfermos asintomáticos. El uso del índice aumentó el 32,7% los casos de riesgo coronario alto. Se halló asociación positiva de la enfermedad con edad, tabaquismo, hipercolesterolemia, sedentarismo, microalbuminuria y enfermedad cardiovascular, y negativa con el consumo de alcohol.

*Conclusiones:* El uso del índice tobillo-brazo es aconsejable para el diagnóstico de esta enfermedad, dada la baja prevalencia de formas sintomáticas y su capacidad para cambiar el riesgo coronario estimado. Se

* Corresponding author: Centro de Salud Villanueva Norte, Pl. Salamanca 9, 06700 Villanueva de la Serena, Badajoz, Spain.
*E-mail address:* felixredondofj@gmail.com (F.J. Félix-Redondo).

1885-5857/$ – see front matter © 2012 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.rec.2012.03.007

debería adaptar los grupos de cribado a la población española. Tabaquismo e hipercolesterolemia son los principales factores de riesgo.


**Abbreviations**

ABI: ankle-brachial index
PAD: peripheral arterial disease

## INTRODUCTION

Peripheral arterial disease (PAD) comprises a wide-ranging set of syndromes characterized by stenosis, of atherosclerotic origin in most cases, of noncoronary arteries. This term is now used mainly to describe disease of the arteries in the legs.[1]

The interest in this disease in recent years is due to the high prognostic importance for predicting arteriosclerotic disease in other arterial territories in organs such as the heart or brain.[2] Given that most of the population affected is asymptomatic,[1] it is recommended to focus on subclinical forms.[1,2] Detection of such conditions can be used to improve the predictions of the current cardiovascular risk functions,[3] and it seems that preventive therapy decreases the risk of death.[4]

An easy, reproducible, and cheap method for detecting arterial stenosis, with a high predictive value, is available: the ankle-brachial index (ABI).[5] The prevalence of PAD is varies widely, and depends on the origin of the population, the age range, and associated cardiovascular risk.[1] In Spain, only 3 population studies are available, 2 in the Catalonian population[6,7] and 1 on a countrywide level.[8] The interest in the present study lies, first, in determining how the disease is distributed and the associated risk factors in a sample of the general population in a region with a cardiovascular mortality higher than the national average,[9] and second, in helping establish how and among which subjects screening should be done, given the current lack of consensus.[10,11]

The primary objective of the study was to determine the prevalence of PAD by measuring the ABI in the general population. The secondary objectives were to assess the diagnostic yield of the Edinburgh questionnaire, the current proposals for screening of the asymptomatic population, the ability of the ABI to modify the estimated risk of ischemic heart disease, and the association of the disease with risk factors.

## METHODS

### Study Design and Population

This was a descriptive cross-sectional study of a population-based sample, representative of a health area in Extremadura, Spain. The study formed part of a broader one that aimed to define the prevalence of cardiovascular risk factors and subclinical arteriosclerotic disease in the population of Extremadura (Hermex study). A detailed description of the methods, response rates to the questionnaire, and demographic data has already been published.[12] Briefly, between 2007 and 2009 a sample of the population between 25 and 79 years of age, randomly selected from the database of the health system in the region of Extremadura, was studied. The database has universal coverage (99.4%). The sample was taken from 16 populations in the Don Benito-Villanueva de la Serena health area in Badajoz. The target population was 75 455 inhabitants. The study was approved by the ethics committees of *Hospital Don Benito-Villanueva* (Don Benito) and *Hospital Infanta Cristina* (Badajoz). Pregnant women, institutionalized subjects, those with serious or terminal illness, and those who were not resident in the aforementioned area were excluded. Eligible participants had to give their informed consent to participate. A sample size of 2400 subjects was calculated to be necessary to estimate the prevalence of different characteristics of the population, with a maximum degree of uncertainty and an accuracy of 2%. Once subjects who did not meet the inclusion criteria had been excluded, there were 3521 eligible subjects. Of these, 2833 (80.5%) participated. Participation rates were similar in all age ranges and both sexes, except in the youngest 10-year age group, where there was a lower representation of men compared to the study population. One subject was excluded from the ABI analysis because this parameter was not measured. Another was excluded because both legs had been amputated due to ischemia.

Of the 688 who did not wish to participate, 58.2% were men ($P$=.01). The mean age was 50.4 (16.4) years. There were no differences in response with regards to age ($P$=.77) among those who participated. Of those who did not participate, it was possible to survey other sociodemographic factors and cardiovascular risk in 458 (66.6%). The results are compared with those of the participants in Table 1.

### Measurements

Surveys were conducted of cardiovascular disease (ischemic heart disease or stroke) and risk factors,[13] including pharmacologic treatment, whether antiplatelet or anticoagulation therapy was given, the Edinburgh questionnaire for detecting intermittent

**Table 1**
Comparison of Sociodemographic Variables and History of Risk Factors or Ischemic Heart Disease Between Participants and Nonparticipants

| Variables | Participants (n=2833) | Nonparticipants (n=688) |
|---|---|---|
| *Age, years* | 51.2 (14.7) | 50.3 (16.2) |
| *Male, %* | 46.5 | 53.8 |
| *Results* | Hermex study, n=2833 | Survey of nonparticipants, n=458 |
| *Level of education, %* | | |
| Illiterate | 12.7 | 12.7 |
| Primary education | 54.2 | 56.8 |
| Secondary/baccalaureate | 20.8 | 14.8 |
| Further education | 12.3 | 10.5 |
| No response | — | 5.3 |
| *Current tobacco use, %* | 31.6 | 30.8 |
| *Ex-smokers, %* | 22.3 | 20.5 |
| *History[a] of hypertension, %* | 29.2 | 20.1 |
| *History[a] of DM, %* | 10.8 | 9.0 |
| *History[a] of hypercholesterolemia, %* | 27.7 | 15.5 |
| *History[a] of IHD,[b] %* | 3.0 | 2.0 |

DM, diabetes mellitus; IHD, ischemic heart disease.
[a] Known risk factors only.
[b] Angina or infarction.

claudication,[14] the Minnesota Leisure-Time Physical Activity Questionnaire,[15,16] and the frequency of alcohol consumption in the previous week. Data were collected on anthropometric parameters, blood pressure (3 measurements in the same arm), and safety laboratory parameters from morning blood samples and urine samples taken in fasting conditions, after nighttime rest.

The ABI was measured according to current recommendations.[1] After 5 min at rest in supine decubitus, and with the limbs bare, an inflatable sleeve was placed on the brachial area of the right arm, 2 cm above the elbow, and on both legs below the knee, 2 cm above the malleoli. Systolic blood pressure was measured in each limb by a Doppler technique (HADECO® Minidop ES 8 Mhz). For the legs, the pressure in the posterior and pedial artery were also collected. The ABI was calculated for each leg as the ratio between the systolic pressure obtained in the ankle (the highest obtained between the tibial artery and the pedial artery) and the right arm. Only one arm was used for the measurement to optimize the examination time of the participants, due to the large number of variables to be collected and recorded. The representative ABI for each individual was taken to be the figure for the leg with the lowest ABI.

All surveys and examinations performed were similar to those done in previous studies,[6,7] and were performed in health centers and outpatient clinics for each study area by 2 nurses who had been trained to use the equipment according to the study protocol.

## Variables

The following were taken into account in the analysis: body mass index (BMI), with a cutoff of BMI≥30 to define obesity and history of hypertension, diabetes, or hypercholesterolemia. These latter were considered present if previously diagnosed by a physician or the patient was receiving pharmacological treatment for these conditions or had a mean blood pressure in the second and third measurement of ≥140/90 mmHg, fasting blood glucose≥126 mg/dL, or total cholesterol 240 mg/dL, respectively. Other variables considered were presence of metabolic syndrome,[17] renal function estimated according to the Modification of Diet in Renal Disease-4 function[18] with a cutoff of 60 mL/min to define renal insufficiency, urinary albumin excretion according to the albumin/creatinine ratio in the first morning miction,[19] sedentary lifestyle if participants answered in the Minnesota questionnaire that they did not do regular leisure time physical exercise, and alcohol consumption if any alcohol had been consumed in the past week. In addition, measurements were taken of systolic and diastolic blood pressure, pulse pressure, blood glucose levels, glycohemoglobin, low-density lipoprotein cholesterol (LDL-C) measured directly, high-density lipoprotein cholesterol (HDL-C), and triglycerides.

Presence of PAD was considered for ABI<0.90 or if the individual had a history of revascularization or amputation due to ischemia. Symptomatic PAD was considered when intermittent claudication was detected in the Edinburgh questionnaire, both with typical location (calves) and atypical location (buttocks and thighs). The diagnostic capacity of this questionnaire for detecting PAD was assessed by calculating the sensitivity, specificity, positive and negative predictive values, and kappa index using the ABI as the reference standard. This analysis was performed for the whole sample, and also only for individuals aged over 59 years to determine whether the validity of the test increased beyond this age, given that the predictive values depend on the prevalence of the disease. It also classified the sample according to 4 prognostic categories of ABI (<0.90, 0.90-0.99, 1.00-1.40, and >1.40).[2]

Although ABI values above 1.40 have been associated with an increased cardiovascular risk,[3] these subjects were not included in the diagnosis of PAD,[1] as the pathophysiological process is not stenosis itself and such values could not be considered evidence of stenosis.[1,20]

To assess the capacity to detect asymptomatic forms according to the current population screening recommendations,[20] we calculated how many cases would not be detected because they would lie outside the groups of special risk. These were defined as age≥70 years, age 50-69 years with a history of smoking or diabetes, and those with a moderate risk of cardiovascular disease defined by a Framingham equation score between 10% and 19%. For this last definition, we used the tables calibrated for Spain[21] between the risk levels of 5% and 9.9%, as has been recently recommended by the authors of the calibration study,[22] to define intermediate risk. In addition, cardiovascular risk was assessed according to the same tables for all subjects aged between 35 years and 74 years with no history of cardiovascular vascular disease, and classified as low risk (<5%), intermediate risk (5%-9.9%), and high risk (≥10%) to determine in how many subjects detection of ABI<0.90 reclassified the individuals into the high-risk category.[2,3]

## Statistical Analysis

Continuous variables were expressed as mean (standard deviation) or median [interquartile range] according to whether the variable was normally distributed or not. Discrete variables were presented according to their absolute and relative frequency, with the respective 95% confidence interval (95%CI). The differences in means were tested using the Student *t* test and the Mann-Whitney U test when the variable did not follow a normal distribution. The differences between proportions were estimated using the chi-square test or Fisher exact test.

A binary logistic regression model was constructed to estimate the independence and strength of association between various independent variables and PAD. The model included variables of epidemiological interest, those with a significant association in the bivariate analysis ($P<.05$), and others that affected the coefficients of any of the other remaining variables by at least 20%. The variables were as follows: age, sex, active smoker, ex-smoker, hypertension, diabetes, hypercholesterolemia, BMI, alcohol consumption, sedentary lifestyle, albuminuria, and previous cardiovascular disease. Variables that maintained a significant level of association, those of undoubted epidemiological interest (sex), and others recognized in the literature as etiologic factors for PAD were retained in the model. Others for which there might be collinearity because of a strong association (for example, risk factors and their treatment, or biological parameters that define these risk factors) were not included in order to avoid an overadjustment of the model and to comply with the principle of parsimony.

# RESULTS

The mean age of the sample was 51.2 (14.7) years, and 46.5% were men. There was 1 case of leg amputation due to ischemia and 2 cases of revascularization by aortofemoral surgery, all in men. These were considered diagnostic of PAD. The prevalence of PAD was 3.7% (95%CI, 3.0-4.5), and was higher in men (5.0%; 95%CI, 3.9%-6.3%) than in women (2.6%; 95%CI, 1.8%-3.5%); $P$=.001. Approximately 20% of the subjects had ABI 0.90 to 0.99 and 1.3% had ABI>1.40, with a predominance in women (Fig. 1). Prevalence increased with age, both in the overall sample and by sex ($P<.001$) with a significant increase ($P<.01$) in those aged over 60 years (Fig. 2). The cumulative prevalence in subjects aged ≥50, ≥60, and ≥70 years was 6.2%, 9.1%, and 13.1%, respectively. The prevalence adjusted for the world population was 2.6% (95%CI,

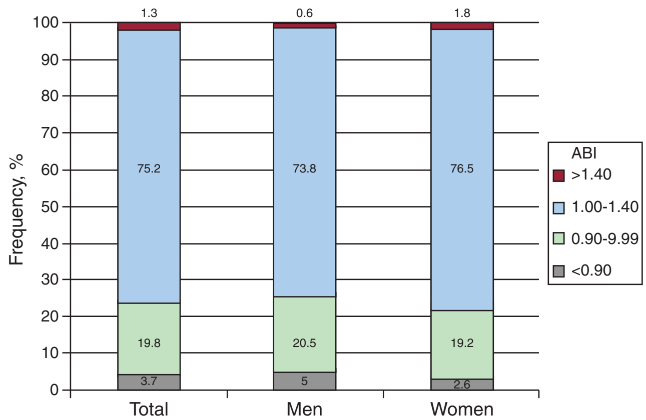


**Figure 1.** Prevalence according to ankle-brachial index categories of prognostic interest. ABI, ankle-brachial index.

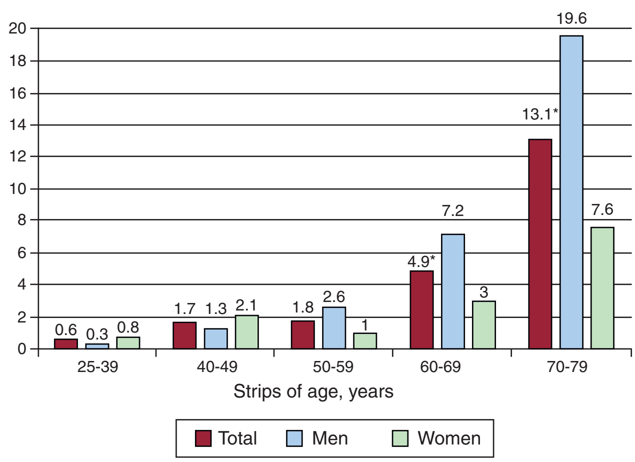


**Figure 2.** Prevalence of peripheral arterial disease according to ankle-brachial index<0.90 by 10-year age groups. *$P<.01$ with respect to preceding 10-year age group.

2.1%-3.1%); among men it was 3.5% (95%CI, 2.7%-4.3%) and among women 1.9% (95%CI, 1.3%-2.5%).

Table 2 shows the characteristics and risk factors according to presence of PAD by sex. Among men, PAD was associated with a higher prevalence of traditional risk factors, with receiving pharmacological treatment for these conditions, and with microalbuminuria, estimated renal insufficiency, previous cardiovascular disease, and symptoms of intermittent claudication. Incidence also increased with age, as did levels of blood glucose, glycohemoglobin, systolic blood pressure, pulse pressure, microalbuminuria, and estimated cardiovascular risk. In contrast, an inverse association was found with glomerular filtration, alcohol consumption, and LDL-C levels. Among women, it was positively associated with all risk factors except smoking and metabolic syndrome, as well as with age, BMI, glycohemoglobin, systolic blood pressure, pulse pressure, LDL-C, trigylcerides, microalbuminuria, history of cardiovasular disease, and symptoms of intermittent claudication. More men and women with PAD received antiplatelet therapy than the study population, and women also received more anticoagulant therapy.

Overall, 1.6% of the subjects responded positively to the Edinburgh questionnaire, with no differences between sexes ($P$=.438) (Table 3), but this rate was reduced to 0.5% when confirmed by ABI<0.90. PAD, understood as ABI<0.90, was symptomatic according to the questionnaire in 13.3% (95%CI, 6.8%-19.8%) of the cases, and more frequently positive in men (16.7%) than in women (7.7%), with no statistically significant differences ($P$=.191). The sensitivity of the questionnaire to detect PAD was 13.3%, the specificity was 96.7%, the positive predictive value was 31.8%, and the negative predictive value was 96.7% ($\kappa$=0.170). These same parameters for age $\geq$60 years did not show an appreciable improvement (Table 3).

With regard to screening for ABI, in groups of greater risk than proposed by the current recommendations[20] 29.6% of the asymptomatic cases were not detected, and most of them (76.2%) corresponded to subjects younger than 50 years.

The prevalence of PAD increased with estimated risk category for ischemic heart disease (low, 1.6%; intermediate, 3.2%; high, 9.7%; $P<.001$) overall and by sex (men: low, 1.7%; intermediate, 3%; high, 9.8%; $P<.001$; women: low, 1.5%; intermediate, 3.7%; high, 9.5%; $P<.01$). A value of ABI<0.90 led to a change in risk category for ischemic heart disease in 37 subjects, resulting in an increase in prevalence of the high risk classification of 32.7%, 16.4% among men and 90.5% among women (Table 4).

In the multivariate analysis (Table 5), PAD was positively and independently associated with age, current and past tobacco consumption, hypercholesterolemia, albuminuria, sedentary lifestyle, and history of cardiovascular disease, and negatively associated with alcohol consumption, adjusted by sex, BMI, history of hypertension, and diabetes. Sex lost the association with the inclusion of tobacco use whereas diabetes and hypertension lost their association with the inclusion of age.

## DISCUSSION

The present study showed that the prevalence of PAD in the general Spanish population was higher and appeared earlier among men and that it increased substantially with age, particularly from 60 years onwards. Symptomatic cases did not exceed 20% of the sample, and the yield was low when the questionnaires were the only means of detecting the disease. We have also shown that measuring the ABI increases the prevalence in subjects with a high estimated risk of ischemic heart disease, particularly among women, and that the current screening guidelines for asymptomatic cases leaves approximately 30% of cases undiagnosed. The main risk factors associated with presence of PAD are tobacco use and hypercholesterolemia.

### Prevalence of Peripheral Arterial Disease

The prevalence of this disease varies greatly according to the age range studied, as most cases are concentrated in the last stages of life. The prevalence found in this study (3.7%) is similar to that of the other studies in Spain if we stratify by age (Fig. 3) and also to that found in the United States National Health and Nutrition Examination Survey[23] in individuals older than 40 years (4.3% vs 4.8% in that study) and in individuals aged between 70 and 80 years (14.5% vs 13.1%). The prevalence is higher among men, given the association with risk factors[12] and the onset is at younger ages than in women; the greatest increase among men occurs from 60 years onwards whereas the main increase is from 70 years onwards in women. A higher prevalence than in other studies was expected.[6,7] Those studies showed a lower association with traditional risk factors,[24] but protective risk factors against the disease could be implicated, such as HDL-C concentrations, which were highest in our population,[24] or other unknown protective factors.

**Table 2**
Demographic, Anthropometric, and Clinical Characteristics Associated With the Presence of Peripheral Arterial Disease According to Ankle-Brachial Index<0.90, by Sex

| | Male | | | Female | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | ABI<0.90 | ABI≥0.90 | *P* | ABI<0.90 | ABI≥0.90 | *P* | ABI<0.90 | ABI≥0.90 | *P* |
| Subjects | 66 (5.0) | 1249 (95.0) | — | 39 (2.6) | 1477 (97.4) | — | 105 (3.7) | 2726 (96.3) | — |
| Age, years | 68.5±10.9 | 50.4±14.2 | <.001 | 63.5±15.3 | 50.8±14.7 | <.001 | 66.6±12.9 | 50.6±14.5 | <.001 |
| Hypercholesterolemia | 48 (72.7) | 481 (38.5) | <.001 | 22 (56.4) | 545 (36.9) | .013 | 70 (66.7) | 1026 (37.7) | <.001 |
| Treatment for hypercholesterolemia | 36 (54.5) | 187 (15.0) | <.001 | 12 (30.8) | 237 (16.0) | .014 | 48 (45.7) | 424 (15.6) | <.001 |
| Hypertension | 52 (78.8) | 531 (42.5) | <.001 | 26 (66.7) | 513 (34.7) | <.001 | 78 (74.3) | 1044 (38.3) | <.001 |
| Treatment for hypertension | 37 (56.1) | 284 (22.7) | <.001 | 21 (53.8) | 356 (24.1) | <.001 | 58 (55.2) | 640 (23.5) | <.001 |
| Diabetes | 23 (34.8) | 182 (14.6) | <.001 | 12 (30.8) | 182 (12.3) | .001 | 35 (33.3) | 364 (13.4) | <.001 |
| Treatment for diabetes | 19 (28.8) | 83 (6.6) | <.001 | 8 (20.5) | 102 (6.9) | .001 | 27 (25.7) | 185 (6.8) | <.001 |
| Tobacco use[a] | 59 (89.4) | 877 (70.2) | .001 | 11 (28.2) | 576 (39.0) | .172 | 70 (66.7) | 1453 (53.3) | .007 |
| Obesity[b] | 32 (48.5) | 463 (37.1) | .062 | 23 (59.0) | 471 (31.9) | <.001 | 55 (52.4) | 934 (34.3) | <.001 |
| MS | 30 (45.5) | 403 (32.3) | .026 | 18 (46.2) | 542 (36.7) | .227 | 48 (45.7) | 945 (34.7) | .020 |
| Blood glucose, mg/dL | 111.5 [99.8-138.3] | 102.0 [95.0-112.0] | <.001 | 102.0 [89.0-120.0] | 95.0 [89.0-104.0] | .067 | 103.5 [88-119] | 99.0 [90.5-107.5] | <.001 |
| $HbA_{1c}$, % | 6.0±1.4 | 5.2±0.8 | <.001 | 5.6±1.2 | 5.1±0.8 | .028 | 5.8±1.3 | 5.2±0.8 | <.001 |
| SBP, mmHg | 146.9±20.4 | 132.2±18.7 | <.001 | 139.9±27.4 | 121.5±23.1 | <.001 | 144.3±23.4 | 126.4±21.9 | <.001 |
| DBP, mmHg | 76.4±11.1 | 78.9±10.1 | .055 | 77.4±11.1 | 74.4±11.1 | .087 | 76.8±11.1 | 76.4±10.8 | .735 |
| PP, mmHg | 70.5±19.8 | 53.3±15.1 | <.001 | 62.4±25.9 | 47.1±17.5 | .001 | 67.5±22.5 | 50.0±16.7 | <.001 |
| LDL-C, mg/dL | 114.4±33.6 | 124.5±32.2 | .014 | 133.8±39.9 | 117.6±30.7 | .001 | 121.6±37.1 | 120.7±31.6 | .786 |
| HDL-C, mg/dL | 49.2±12.3 | 51.8±13.4 | .120 | 58.9±14.7 | 60.7±14.1 | .427 | 52.8±14.0 | 56.6±14.5 | .008 |
| TGC, mg/dL | 113.5 [78.0-147.0] | 103.0 [75.0-153.0] | .355 | 101.0 [79.0-147.0] | 84.0 [62.0-115.0] | .003 | 113.5 [75.5-151.5] | 93 [60.5-125.5] | .001 |
| BMI | 30.3±5.9 | 29.1±4.6 | .054 | 32.2±8.3 | 28±5.7 | .002 | 31±6.9 | 28.5±5.3 | <.001 |
| GFR, mL/min/1.73 $m^2$ | 94.4±18.8 | 87.2±21.1 | .002 | 93.4±20.9 | 86.6±23.7 | .045 | 87±22 | 93.9±20 | .001 |
| UAE, mg/g[c] | 6.2 [2.5-22.9] | 2.4 [1.6-4.4] | <.001 | 4.7 [2.7-9.7] | 2.9 [1.8-5.2] | .004 | 4 [0.8-7.1] | 2.6 [1.1-4.1] | <.001 |
| Sedentary lifestyle[d] | 10 (15.2) | 113 (9.0) | .097 | 2 (5.1) | 14 (0.9) | .062[e] | 12 (11.4) | 127 (4.7) | .002 |
| Alcohol | 32 (48.5) | 800 (64.1) | .011 | 3 (7.7) | 188 (12.7) | .467[e] | 35 (33.3) | 988 (36.2) | .542 |
| GFR <60 L/min[f] | 5 (7.6) | 31 (2.5) | .013 | 4 (10.3) | 70 (4.7) | .119[e] | 9 (8.6) | 101 (3.7) | .011 |
| Microalbuminuria[g] | 16 (24.2) | 70 (5.6) | <.001 | 7 (17.9) | 56 (3.8) | <.001 | 23 (21.9) | 126 (4.6) | <.001 |
| IC | 11 (16.7) | 12 (1.0) | <.001 | 3 (7.7) | 18 (1.2) | .001[e] | 14 (13.3) | 30 (1.1) | <.001 |
| Risk of ischemic heart disease,[h] % | 7.1 [2.6-11.3] | 3.4 [1.9-6.0] | .001 | 2.5 [1.1-5.1] | 1.7 [0.8-3.2] | .071 | 4.2 [0.7-7.9] | 2.4 [0.8-4.1] | <.001 |
| History[i] of CVD | 21 (31.8) | 64 (5.1) | <.001 | 3 (7.7) | 42 (2.8) | .001[e] | 24 (22.9) | 106 (3.9) | <.001 |
| Antiplatelet therapy | 30 (45.5) | 83 (6.6) | <.001 | 7 (17.9) | 90 (6.1) | .003 | 37 (35.2) | 173 (6.3) | <.001 |
| Anticoagulants | 3 (4.5) | 25 (2.0) | .163 | 6 (15.4) | 25 (1.7) | <.001 | 9 (8.6) | 50 (1.8) | <.001 |

ABI, ankle-brachial index; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; $HbA_{1c}$, glycohemoglobin; HDL-C, high-density lipoprotein cholesterol; IC, intermittent claudication; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; PP, pulse pressure; TGC, triglycerides; UAE, urinary albumin excretion.
Data are expressed as no. (%), mean±standard deviation or median [interquartile range].
[a] Tobacco use, past or present history of smoking.
[b] BMI≥30.
[c] Using Modification of Diet in Renal Disease-4 formula.
[d] Lack of leisure time physical activity;
[e] Fisher exact test.
[f] Albumin/creatinine ratio.
[g] Albumin/creatinine ratio≥22 mg/g (men) ≥31 mg/g (women).
[h] Age 35-74 years without CVD.
[i] Ischemic heart disease or stroke.

**Table 3**
Prevalence of Intermittent Claudication and Diagnostic Value of the Edinburgh Questionnaire for Detecting Peripheral Arterial Disease

| Prevalence of Intermittent Claudication | Male | Female | Total |
|---|---|---|---|
| *Total sample* | 23 (1.7) [1.0-2.25] | 21 (1.4) [0.8-2.0] | 44 (1.6) [1.1-2.0] |
| *Confirmed for ABI<0.90 in total sample* | 11 (0.8) [0.3-1.3] | 3 (0.2) [0-0.4] | 14 (0.5) [0.2-0.8] |
| *Only among those with ABI<0.90* | 11 (16.7) [7.7-25.7] | 3 (7.7) [0-35.7] | 14 (13.3) [6.8-19.8] |
| *Diagnostic Value of the Edinburgh questionnaire* | | | |
| Total sample | Sensitivity, 13.3%; specificity, 96.7%; PPV, 31.8%; NPV, 96.7%; κ 0.170 (95%CI, ±0.084); *P*<.001 | | |
| Age≥60 years | Sensitivity, 16.5%; specificity, 97.3%; PPV, 38.2%; NPV, 92.1%; κ=0.186 (95%CI, ±0.104); *P*<.001 | | |

95%CI, 95% confidence interval; ABI, ankle-brachial index; NPV, negative predictive value; PPV, positive predictive value.
Unless otherwise indicated, data are presented as no. (%) [95%CI].

**Table 4**
Differences (Relative Increase) in the Classification of Estimated Risk for Ischemic Heart Disease After Use of the Ankle-Brachial Index

| Level of calibrated Framingham risk[19,20] | Distribution by risk categories* (n=2105) | | |
|---|---|---|---|
| | Without ABI | With ABI | Difference, % |
| *< 5%* | 1651 (78.4) | 1625 (77.2) | –1.6 |
| *5%-10%* | 341 (16.2) | 330 (15.7) | –3.2 |
| *≥10%* | 113 (5.4) | 150 (7.1) | 32.7 |
| *Men (n=977)* | | | |
| <5% | 653 (66.8) | 642 (65.7) | –1.7 |
| 5%-10% | 232 (23.7) | 225 (23) | –3.1 |
| ≥10% | 92 (9.4) | 110 (11.3) | 16.4 |
| *Women (n=1128)* | | | |
| <5% | 998 (88.5) | 983 (87.1) | –1.5 |
| 5%-10% | 109 (9.7) | 105 (9.3) | –3.8 |
| ≥10% | 21 (1.9) | 40 (3.5) | 90.5 |

ABI, ankle-brachial index.
Detection of ABI<0.90 classified the subject as risk ≥10%.
* Population between 35 and 74 years with no history of cardiovascular disease.

**Table 5**
Multivariate Analysis of the Variables Associated With Peripheral Arterial Disease By Binary Logistic Regression

| Variables | OR (95%CI) | *P* |
|---|---|---|
| Age | 1.09 (1.07-1.11) | <.001 |
| Ex-smoker[a] | 3.11 (1.63-5.93) | .001 |
| Smoker[b] | 4.48 (2.23-8.98) | <.001 |
| Hypercholesterolemia | 2.06 (1.31-3.22) | .002 |
| History of CVD | 2.05 (1.15-3.64) | .014 |
| Albuminuria[c] | 2.51 (1.41-4.45) | .002 |
| Sedentary lifestyle[d] | 2.48 (1.22-5.01) | .012 |
| Alcohol[e] | 0.53 (0.31-0.89) | .017 |

95%CI, 95% confidence interval; CVD, cardiovascular disease; OR, odds ratio.
Model adjusted for all variables that appear in the table along with sex, body mass index, diabetes, and hypertension. Calibration of the model (Brier score) = 0.032. Discrimination of fully adjusted model (area under receiver operating characteristics curve) = 0.851 (0.809-0.893).
a More than 1 year without smoking.
b Current smoker or smoked within the last year.
c Albumin/creatinine ratio ≥22 mg/g (men) or ≥31 mg/g (women).
d Lack of leisure time physical activity.
e Consumption of alcohol in the past week.

## Prevalence of Symptomatic Peripheral Arterial Disease

In a substantial number of cases PAD is asymptomatic, and this varies between studies because it depends on regular physical activity of the subjects.[20] In the Framingham Offspring Study cohort,[25] symptomatic forms accounted for 56% of cases in men and 18% in women. In the Spanish studies, with the exception of the ARTPER study (32%),[7] symptomatic forms accounted for much lower percentages of the overall cases: ESTIME,[8] 14%; REGICOR,[6] 13.7%, and the present study, 13.3%. In all cases the percentage was lower for women. Thus, the Edinburgh questionnaire has limited diagnostic value as a screening test in Spain and above all among women. The value does not increase even when used in cohorts with greatest prevalence, such as from 60 years onwards.

## Screening the Asymptomatic Population

With the current recommendations,[20] a substantial part of the asymptomatic forms would go undetected, and so it would be advisable to adapt to the Spanish population tools that identify subjects with a greater risk of having PAD. Recent proposals such as those of Ramos et al.[26] could be very useful in clinical practice.

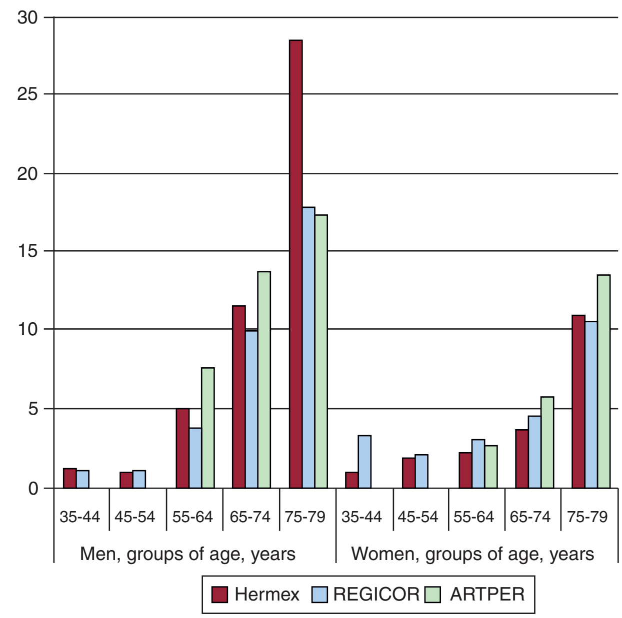


**Figure 3.** Comparison of peripheral arterial disease prevalence according to ankle-brachial index<0.90 by 10-year age groups with the REGICOR[6] and ARTPER[7] studies. Cases of ankle-brachial index>1.40 are excluded from the overall population of the 3 studies.

## Value of Ankle-brachial Index in Reclassification of Risk Category

The ABI increased the prevalence of the high-risk category for ischemic heart disease by 16.4% in men and 90.5% in women. These figures were similar to those obtained in the ARTPER study[27] (19.1% in men and 151.5% in women). This shows the usefulness of having a test to improve the estimated risk, although it would be necessary to follow the cohorts and record cardiovascular events to confirm the validity of this change in the Spanish population, as demonstrated in other studies.[3] However, inclusion of subjects with ABI 0.90 to 0.99 and ≥1.40 was not considered. Such individuals also have an increased risk of cardiovascular morbidity and mortality[3] and these accounted for more than 20% of the population in the present study.

## Variables Associated With Peripheral Arterial Disease

All the traditional risk factors have been etiologically related to PAD, although the different age ranges and risk profiles of the populations studied may show different strengths of association with these factors.[23] In the present study, there was an association with all of them except for obesity in men and with metabolic syndrome and tobacco use in women. The lack of association with tobacco use in women, one of the main etiological factors of the disease, could be explained by the very limited number of smokers in the most elderly cohort (data not shown). The negative association with LDL-C levels in men is due to the higher proportion of subjects who were taking statins: this relationship disappeared when those who were taking these drugs were excluded (data not shown). Of note, however, for its novelty is the association with urinary albumin excretion and estimated glomerular filtration rate, which is only apparent in Spain in the population with hypertension,[28] lack of leisure time physical activity, or alcohol consumption. In the multivariate analysis, there was only an association between the traditional risk factors of age, history of tobacco use, and hypercholesterolemia. It is noteworthy that including a history of tobacco use led to the disappearance of the excess risk among men. It is therefore a point of possible importance for evaluating the possible impact of controlling this risk factor for PAD in the population. The lack of association with other recognized risk factors for PAD, such as diabetes or hypertension, had already been observed in other studies.[6,25] This may be due to the limitations of cross-sectional studies themselves, to an insufficient number of individuals with these conditions, or to the different risk for populations with short exposure times to these risk factors or their low intensity. The association with other subclinical or symptomatic vascular diseases is a constant feature in most studies,[6–8,20,21] and shows that arteriosclerosis affects the entire vascular territory and that ABI can help detect the condition earlier.[3] The association with sedentary lifestyle has also been described in other studies in Spain[7]; however, we should be cautious in interpreting this observation in this cross-sectional study, given that this association may be due to a lower functional capacity of subjects with PAD. Finally, the negative association found with alcohol consumption could be explained by the already known benefits of lipid profile and coagulation,[29] as prospective studies have shown a negative association with the disease.[30]

### Strengths and Limitations of the Study

The strength of this study lies in the fact that the epidemiological information for PAD was collected for a wide range of ages, representative of the general population, and originating from a region of Spain with a high prevalence of risk factors.[12,24] The use of the same methodology as in the other Spanish population studies means that they can be readily compared.

With regard to limitations, in addition to the intrinsic design of the study, in which the associations found cannot be interpreted as a etiological relationship, there is the fact that systolic blood pressure in the right arm only was used as the reference for the pressures obtained in the lower limbs; this may reduce the number of cases of PAD detected. The low prevalence of this disease in women could limit the capacity for demonstrating certain associations in this group. The sample obtained is representative of a health area, and so the results cannot be projected to other populations, although there are no indications that it might be different from the rest of the region. The presence of a young population up to 25 years, along with the absence of individuals over 79 years, may condition the prevalence of the disease found, given the strong association with age. The lack of participation by 20% of the eligible population may have influenced the results, although the survey filled out by two-thirds of those who did not participate did not suggest that this would be a determining factor.

## CONCLUSIONS

The prevalence of PAD is similar to that found in other Spanish studies. The Edinburgh questionnaire for detecting intermittent claudication is of very limited use when used alone for diagnosing PAD. The use of ABI modified the estimated risk of ischemic heart disease in an appreciable number of patients. Both these points, the low prevalence of symptomatic forms and the capacity to improve the estimation of coronary risk, suggest that this diagnostic test should be used. However, the criteria that define the risk groups should be adapted to the Spanish population to improve its diagnostic value. Tobacco use and hypercholesterolemia are the main risk factors that showed an association with the disease; therefore, we should step up therapeutic interventions in these risk factors.

## FUNDING

National Plan for Scientific Investigation 2004-2007 (PI 071218), grants for emerging groups (EMER 07/046), grants for improving research (INT 07/289, 09/030), Río Hortega Contract (CM08/00141) from the *Instituto de Salud Carlos III*, grant from the Integral Plan of Extremadura for Cardiovascular Diseases, Fundesalud, *Junta de Extremadura* (Regional Government of Extremadura).

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for management of patients with peripheral arterial disease. J Am Coll Cardiol. 2006;47:1–192.
2. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA. et al. ., 2010 ACCF/AHA Guideline for assessment of cardiovascular risk in asymptomatic adults. Circulation. 2010;122:e584–636.
3. Ankle brachial index collaboration. Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.
4. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease. Circulation. 2011;124:17–23.
5. Fowkes FG. The measurements of atherosclerosis peripheral arterial disease in epidemiological surveys. Int J Epidemiol. 1988;17:248–54.
6. Ramos R, Quesada M, Solanas P, Subirana I, Sala J, Vila J, et al. Prevalence of symptomatic and asymptomatic peripheral arterial disease and the value of the ankle-brachial index to stratify cardiovascular risk. Eur J Vasc Surg. 2009;38:305–11.
7. Alzamora MT, Forés R, Baena-Díez JM, Pera G, Totan P, Sorribes M, et al. The peripheral arterial disease study (PERART/ARTPER): prevalence and risk factors in the general population. BMC Public Health. 2010;10:38.
8. Blanes JL, Cairols MA, Marrugat J. Prevalence of peripheral arterial disease and its associated risk factors in Spain: The ESTIME Study. Int Angiol. 2009;28:20–5.
9. Tasas estandarizadas de mortalidad cardiovascular por comunidades. Madrid: Instituto Nacional de Estadística; 2009 [cited 9 Sep 2011]. Available at: http://www.ine.es/inebmenu/mnu_salud.htm
10. Bertomeu-Martínez V, Toro-Solórzano M, Moreno-Arribas J. ¿Debemos determinar el índice tobillo-brazo en el paciente hipertenso o diabético? Rev Esp Cardiol Supl. 2009;9:18D–23D.
11. Mostaza JM, Lahoz C. ¿A quién medir el índice tobillo-brazo? Med Clin (Barc). 2010;135:312–3.
12. Félix-Redondo FJ, Fernández-Bergés D, Pérez F, Zaro MJ, García A, Lozano L, et al. Prevalencia, detección, tratamiento y grado de control de los factores de riesgo cardiovascular en la población de Extremadura Estudio HERMEX. Aten Primaria. 2011;43:426–34.
13. WHO MONICA project principal investigators. The WHO MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. J Clin Epidemiol. 1988;41:105–14.
14. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose questionnaire for use in epidemiological surveys. J Clin Epidemiol. 1992;45:1101–9.
15. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men The MARATHOM investigators. Am J Epidemiol. 1994;139:1197–209.
16. Elosua R, Garcia M, Aguilar A, Molina L, Covas MI, Marrugat J. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish women Investigators of the MARATDON Group. Med Sci Sports Exerc. 2000;32:1431–7.
17. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
18. Levey AS, Greene T, Jusek J, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol. 2000; 11:A1828.
19. Mancia G, De Backer G, Dominiczak A, Renata C, Fagard G, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). J Hypertens. 2007;25:1105–87.

20. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl. 1:S1–70.
21. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordón F, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. Rev Esp Cardiol. 2003;56:253–61.
22. Marrugat J, Vila J, Baena-Díez JM, Grau M, Sala J, Ramos R, et al. Validez relativa de la estimación del riesgo cardiovascular a 10 años en una cohorte poblacional del estudio REGICOR. Rev Esp Cardiol. 2011;64:385–94.
23. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States. Results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110:738–43.
24. Grau M, Elosua R, Cabrera de León A, Guembe MJ, Baena-Díez JM, Vega T, et al. Factores de riesgo cardiovascular en España en la primera década del siglo XXI: análisis agrupado con datos individuales de 11 estudios de base poblacional, estudio DARIOS. Rev Esp Cardiol. 2011;64:295–304.
25. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PWF. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143:961–5.
26. Ramos R, Baena-Díez JM, Quesada M, Solanas P, Subirana I, Sala J, et al. Derivation and validation of REASON: a risk score identifying candidates to screen for peripheral arterial disease using ankle brachial index. Atherosclerosis. 2011;214:474–9.
27. Baena-Díez JM, Alzamora MT, Forés R, Pera G, Torán P, Sorribes M, et al. El índice tobillo-brazo mejora la clasificación del riesgo cardiovascular: estudio ARTPER/PERART. Rev Esp Cardiol. 2011;64:186–92.
28. Mostaza J, Suarez C, Manzano L, Cairols M, García-Iglesias F, Sanchez-Alvarez J, et al. Relationship between ankle-brachial index and chronic kidney disease in hypertensive patients with no known cardiovascular disease. J Am Soc Nephrol. 2006;17 Suppl 3:S201–5.
29. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ. 1999;319:1523–8.
30. Athyros VG, Liberopoulos EN, Mikhailidis DP, Papageorgiou AA, Ganotakis ES, Tziomalos K, et al. Association of drinking pattern and alcohol beverage type with the prevalence of metabolic syndrome, diabetes, coronary heart disease, stroke and peripheral arterial disease in a Mediterranean cohort. Angiology. 2007;58:689–97.