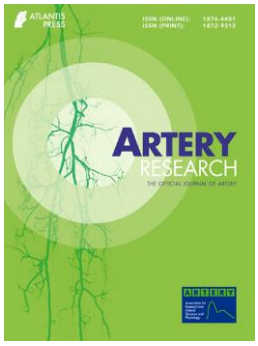

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Gender as a moderator in the relationship between anxiety and carotid intima-media thickness: The PREVENCION study

Diana A. Chirinos [a,*,e], Belissa Salinas-Najarro [b,e], Roberto Paz-Manrique [b,e], Zubair Khan [c,e], Waheed Raja [c,e], Francisco Ibañez [b,e], Fernando Corrales-Medina [a,e], Humberto Zea-Diaz [b,e], Julio A. Chirinos [c,d,e], Josefina Medina-Lezama [b,e]

[a] University of Miami, FL, USA
[b] Santa Maria Catholic University Research Institute, Arequipa, Peru
[c] University of Pennsylvania, PA, USA
[d] Philadelphia VA Medical Center, USA

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Abstract *Background:* Previous studies regarding the association of atherosclerotic risk and anxiety have yielded conflicting results. Carotid intima–media thickness (cIMT) is an early marker of subclinical atherosclerosis and an independent predictor of cardiovascular risk. We aimed to determine the relationship between anxiety and cIMT in Andean Hispanics and examine the moderating effects of gender in this relationship.

Methods: We studied 496 adults enrolled in a population-based study in Peru. cIMT was measured with high-resolution ultrasonography. Anxiety levels were assessed with the HADS anxiety score.

Results: Median anxiety scores were 6 (IQR = 4–8) in men and 8 (IQR = 5–11) in women. We found a significant moderating effect of gender on the association between the HADS anxiety score and cIMT. Among men, the HADS anxiety score was significantly associated with cIMT ($\beta = 0.15$; $P = 0.004$) after adjusting for age, education, employment status, SBP, DBP, fasting glucose, diabetes mellitus, smoking and LDL cholesterol. Other significant predictors of cIMT in men were age ($\beta = 0.60$; $P < 0.001$), SBP ($\beta = 0.16$; $P = 0.023$) and diabetes mellitus ($\beta = 0.12$; $P = 0.033$). The model explained 54% of the population variability in cIMT. The HADS anxiety score was not associated with cIMT in women.

* Corresponding author. Department of Psychology, University of Miami, P.O. Box 248185, Coral Gables, FL 33124-0751, USA. Tel.: +1 305 284 2687.
E-mail address: dchirinos-medina@psy.miami.edu (D.A. Chirinos).
[e] On behalf of the PREVENCION Investigators.

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Conclusions: We found an important moderating effect of gender in the relationship between anxiety and subclinical atherosclerosis. Anxiety was independently associated with subclinical atherosclerosis among Andean Hispanic men, whereas no relationship was found among women. Further studies are required to assess the mechanistic determinants of this association and assess whether interventions to decrease anxiety levels retard the progression of early, subclinical atherosclerosis.

Introduction

Cardiovascular disease (CVD) has emerged as a leading cause of death in Latin America.[1] The identification of modifiable risk factors for early atherosclerosis is important because prevention strategies instituted early in the disease process are likely to have the highest impact in cardiovascular outcomes.

Various previous studies have assessed the association between psychosocial factors and atherosclerotic risk. Most previous studies addressing the relationship between psychosocial factors and atherosclerosis have focused on depression,[2] hostility,[3] type A personality and psychosocial stress,[4] but fewer studies have focused on anxiety. Anxiety and/or trait anxiety has been associated with increased levels of inflammatory markers, coagulation makers,[5] sympathetic activation, oxidative stress and endothelial dysfunction.[6,7] Studies assessing the association between anxiety and atherosclerosis have yielded conflicting results. Kawachi et al. demonstrated an independent association between symptoms of anxiety and the risk of coronary heart disease among community-dwelling men.[8] More recent studies failed to show an association between anxiety and subclinical atherosclerosis,[9,10] and most have assessed by coronary artery calcium quantified by electron beam computed tomography (EBCT). However, data regarding the association between anxiety and other markers of subclinical atherosclerosis is still scarce.

High-resolution carotid ultrasonography can reliably determine the presence or extent of carotid atherosclerosis *in situ*. Common carotid artery intima—media thickness (cIMT) is a well validated marker of subclinical atherosclerosis and the risk of future cardiovascular events.[11,12] Although both coronary calcium and cIMT are measures of atherosclerosis, these are not interchangeable and it has recently been shown that they have different genetic and environmental determinants.[13] Therefore, data are needed regarding the relationship between anxiety and cIMT. Furthermore, given the ethnic diversity in the profile of CVD, varied risk associations and different levels of genetic—environmental interactions in different populations[14] and the potential influence of ethnicity and cultural factors as determinants of emotions and how they are experienced, more research in non-Caucasian populations is needed. In particular, data from South American Hispanic populations regarding the association between anxiety and subclinical atherosclerosis are not available.

Therefore, in this study, we aimed to: [1] Assess the relationship between cIMT and anxiety among Andean Hispanic adults and assess whether this relationship is independent of established cardiovascular risk factors; [2] Examine gender as a moderator in the association between cIMT and anxiety in this population.

Methods

Study population and sampling design

The general objectives and design of the PREVENCION study have been previously published.[15] PREVENCION is a population-based study undertaken in the second largest city in Peru, with a population that is comparable to other urban populations in Peru and resembles urban populations in Andean countries such as Bolivia and Ecuador. This population consists largely of Mestizos ("Mixed race"), with the degree of genetic admixture being predominantly Andean Amerindian (i.e., autochthonous Quechua and Aymara) with only small genetic contributions of Spanish Whites and minimal contributions from West African populations.

The first phase of PREVENCION is designed to determine the prevalence of CVD and cardiovascular risk factors in the adult study population. Details regarding the sampling strategy have been previously published.[15] The sampling frame was based on the most recent population and household National Census[15] and the sampling strategy was probabilistic, multistage, clustered and stratified according to geographic location and socioeconomic status. Following initial contact with participants at their household, a comprehensive evaluation was performed at the study headquarters as previously described.[15,16]

This analysis is based on an ancillary study in which anxiety levels were evaluated among an unselected subsample of PREVENCION study participants composed of 285 women and 211 men (total $n = 496$). The study was approved by the Santa Maria Catholic University Human Research Committee and all participants gave informed consent.

Measurements of cIMT

High-resolution B-mode carotid ultrasonography was performed with a linear-array, 10-MHz transducer in B mode (Sonosite Titan; Sonosite; Bothell, WA). With the subject in the supine position in a quiet room, images were obtained bilaterally from the anterior, posterior and lateral views. Both carotid arteries were examined with the head tilted slightly upward in the mid-line position. The transducer was manipulated so that the near and far walls of the common carotid artery (CCA) were parallel to the transducer

footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1.0 cm proximal to the carotid bulb was identified, and cIMT of the near and far walls were evaluated as the distance between the lumen–intima interface and the media–adventitia interface. If plaques were present in this area, these were included in the measurements. Measurements of cIMT were performed on a frozen frame of a suitable longitudinal image using the Sonocalc software (Sonosite Titan; Sonosite; Bothell, WA), which performs multiple automated or semi automated measurements along 1 cm and averages them, therefore increasing the accuracy of measurements. A single physician conducted the carotid ultrasonic examination. All measurements were performed offline in a blinded fashion.

Assessment of anxiety

The Hospital Anxiety and Depression Scale (HADS) score was used for the evaluation of anxiety.[17] HADS was originally designed to identify caseness of anxiety disorders and depression among non-psychiatric hospital clinics, however it has been found to perform well in somatic, psychiatric and primary care patients as well as in the general population.[18] It consisted of a 7-item anxiety subscale and a 7-item depression subscale. Each item was scored on a 4-point likert scale (0–3 points) giving maximum subscale scores of 21. HADS has been validated in Spanish populations both in Spain[19] and Latin America.[20]

Statistical analysis

Data for continuous variables are presented as means and standard deviation or medians and interquartile range as appropriate. These were compared between groups with the independent *t* test or the Mann–Whitney-*U* test as appropriate. Proportions are presented as percentages and were compared with the χ^2 test. Each variable included in the analyses was tested for internal consistency and normality. If the univariate frequency distributions expressed any non-normal distribution patterns, the data was transformed to correct for the skewness. A natural log transformation was used in order to achieve a normal distribution. Multiple linear regression analyses were used to test the association between anxiety and cIMT. Important control variables (identified previously as predictors of cIMT in this population)[21] such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), impaired fasting glucose (fasting glucose 100–125 mg/dL), current smoking and low-density lipoprotein (LDL) cholesterol levels were included in the models. All tests were two-sided and $\alpha < 0.05$ was considered to be statistically significant. SPSS for Windows version 17 (SPSS, Chicago, IL, USA) was used for all regression analyses. The moderating effects of gender were tested using multiple group analysis within the context of structural equation modeling (SEM). Multiple group analysis in SEM allows assessment of the population heterogeneity in various structure parameters such as variances, covariances and paths. Multiple group analysis requires a multi-step procedure. Initially, a test of baseline model fit is established. The baseline model consisted of a direct path between anxiety and cIMT, and direct paths between all control variables and cIMT. In this baseline model all intercepts and path coefficients were constrained equal between groups. Subsequently, individual path coefficients were unconstrained between groups and model fit was re-assessed. A chi-square difference test was then conducted between these nested models to determine whether parameters can be estimated equally between groups. Mplus version 6.00 was used for all moderation analyses.

Results

The study population consisted of 496 participants (211 men and 285 women). Median age was 51 years. Important demographic, clinical and laboratory characteristics of the study population are shown in Table 1. There was no significant difference in age between men and women in the sample. In this population, men demonstrated a higher prevalence of smoking and alcohol consumption. Men were significantly taller, heavier and demonstrated higher waist circumference, but body mass index was not significantly different between genders. Men demonstrated higher triglyceride levels and significantly lower high-density lipoprotein (HDL) cholesterol. Total cholesterol was slightly lower among men. There were no differences in LDL-cholesterol or the prevalence of diabetes mellitus. There was no significant difference in cIMT between men and women. Women demonstrated a higher median HADS anxiety score compared to men.

HADS score and its correlates

As shown in Table 1, women demonstrated a higher median HADS anxiety score (8; IQR = 5–11) compared to men (6; IQR = 4–8; $P < 0.0001$). The HADS score did not significantly correlate with age, blood pressure, HDL-cholesterol, LDL-cholesterol, triglycerides, current smoking, waist circumference or the presence of diabetes mellitus (Table 2). In multivariate analysis, gender was an independent predictor of the HADS score after adjustment for all these cardiovascular risk factors (Table 2).

The HADS score as a predictor of cIMT

In this sample, the HADS anxiety score was not significantly associated with cIMT (standardized $\beta = 0.04$; $P = 0.239$) in multivariate regression after controlling for age, employment status, education, SBP, DBP, glucose, diabetes mellitus, smoking and LDL-cholesterol. Significant predictors of CIMT were age (standardized $\beta = 0.60$; $P < 0.0001$), SBP (standardized $\beta = 0.17$; $P = 0.001$), glucose (standardized $\beta = 0.07$; $P = 0.028$) and diabetes mellitus (standardized $\beta = 0.09$; $P = 0.006$).

Gender differences

Gender differences were analyzed by testing the regression multivariate model simultaneously across groups constraining the regression paths of each independent variable to be equal for men and women. The constrained model

Table 1 Demographic, clinical and laboratory characteristics of the study population.

	Men (n = 211)	Women (n = 285)	P value
Age, years	50 (38–63)	52 (39–64)	0.43
Current smoking (%)	24.2	13.3	**0.002**
Current alcohol consumption (%)	50.0	18.0	**<0.0001**
Body height, cm	169 (164–174)	156 (152–161)	**<0.0001**
Body weight, Kg	74.0 (68.0–84.7)	63.0 (55.6–71.9)	**<0.0001**
Body mass index, kg/m^2	26.3 (24.2–29.1)	25.9(22.6–29.1)	0.15
Waist circumference, cm	94 (87–101)	86 (78–94)	**<0.0001**
Current use of hormonal contraceptives (%)	–	4.6	–
Systolic blood pressure, mmHg	120 (110–132)	118 (105–131)	0.24
Diastolic blood pressure, mmHg	80 (71–84)	76 (70–82)	**0.02**
Total cholesterol, mg/dL	195 (173–220)	201 (179–230)	**0.04**
HDL cholesterol, mg/dL	43 (37–61)	48 (40–56)	**<0.0001**
LDL cholesterol, mg/dL	117 (100–133)	119 (103–145)	0.18
Triglycerides, mg/dL	183(125–250)	142 (104–194)	**<0.0001**
Diabetes mellitus (%)	7.7	11.4	0.17
Current use of statins (%)	2.8	1.8	0.42
Current use of cholesterol-lowering medication (%)	4.7	3.2	0.37
HADS anxiety score	6 (4–8)	8 (5–11)	**<0.0001**
Carotid intima–media thickness, mm	0.64 (0.55–0.78)	0.63 (0.54–0.74)	0.14

HDL = High density lipoprotein; LDL = Low density lipoprotein. Numbers in bold are statistically significant.

showed adequate fit to the data (χ^2 = 16.25, df = 10, P = 0.093). Individual path coefficients were subsequently unconstrained between groups and model fit was re-assessed. No significant changes in model fit were observed for control variables. However, a model where the HADS anxiety score path coefficient was freely estimated across gender showed significantly better fit to the data (χ^2 difference = 7.61, df = 1, P = 0.006). These results indicated a significant moderating effect of gender on the association between anxiety and cIMT, therefore multiple regression models were fitted for men and women separately. Table 3 shows the results of multiple regression analyses assessing the independent predictors of cIMT in men and women separately.

Among men, the HADS anxiety score was significantly associated with cIMT (standardized β = 0.15; P = 0.004) after adjusting for age, employment status, education, SBP, DBP, fasting glucose, diabetes mellitus, smoking and LDL cholesterol. Other significant predictors of cIMT in men were age (standardized β = 0.60; P < 0.001), SBP (standardized β = 0.16; P < 0.023) and diabetes mellitus (standardized β = 0.12; P = 0.028). Multivariate models that incorporated the HADS Anxiety Score were found to be superior when predicting change in cIMT as evidenced by a significant R square gain (R^2 change for men = 0.02, P = 0.004). The final multivariate model explained 54% of the population variability in cIMT. In contrast, the HADS anxiety score was not independently associated with cIMT in women (Table 3). Significant predictors of cIMT in women included age, DBP and fasting glucose (model R^2 = 0.56).

Results were similar in multivariate regression models that excluded subjects with present carotid plaque

Table 2 Association of various cardiovascular risk factors with the HADS score.

	Univariate analysis			Multivariate analysis (R^2 = 0.05)	
	β	R	P value	β (95%CI)	P value
Age (per 10 years)	0.06	0.03	0.55	−0.25	0.75
Male gender	−1.43	0.19	**<0.0001**	−1.44	**<0.0001**
Systolic blood pressure (per 10 mmHg)	0.08	0.04	0.36	0.01	0.92
Diastolic blood pressure (10 mmHg)	0.12	0.03	0.49	0.13	0.59
HDL-cholesterol (per 10 mg/dL)	0.17	0.05	0.32	0.06	0.74
LDL-cholesterol (per 10 mg/dL)	0.10	0.08	0.064	0.09	0.10
Triglycerides (per 10 mg/dL)	0.02	0.04	0.37	−0.01	0.57
Smoking (current yes or no)	0.15	0.02	0.73	0.35	0.45
Waist circumference (per 10 cm)	−0.06	0.02	0.67	0.09	0.58
Diabetes mellitus[a]	0.17	0.001	0.98	<0.001	0.99

[a] Defined as fasting blood glucose ≥126 mg/dL or use of antidiabetic medications. Numbers in bold are statistically significant.

Table 3 Predictors of (log) carotid intima–media thickness in men and women[†] in multivariate regression.

	Men (R^2 = 0.54)			Women (R^2 = 0.59)		
	Standardized β	*P* value	R^2 increase	Standardized β	*P* value	R^2 increase
Age	0.60	**<0.0001**	0.259	0.59	**<0.0001**	0.174
Systolic blood pressure	0.16	**0.023**	0.013	0.21	**0.001**	0.018
Diastolic blood pressure	−0.02	0.719	0.000	−0.07	0.215	0.003
Fasting glucose (log)	0.03	0.588	0.001	0.13	**0.003**	0.015
Diabetes mellitus[a]	0.12	**0.028**	0.012	0.05	0.253	0.002
Current Smoking	−0.03	0.607	0.001	0.05	0.249	0.001
LDL-cholesterol	0.08	0.136	0.005	0.05	0.254	0.002
HADS anxiety score	0.15	**0.004**	0.020	−0.03	0.540	0.001

[†]Models controlled for socioeconomic variables (education and employment status).
[a] Fasting blood glucose ≥126 mg/dL or use of antidiabetic medications. Numbers in bold are statistically significant.

(i.e., presence of at least one localized echo structure encroaching into the vessel lumen for which the distance between the media–adventitia interface and the internal side of the lesion was ≥1 mm).

Discussion

In this paper, we report on the association between subclinical carotid atherosclerosis and anxiety in an unselected community-based sample of Andean Hispanics. We provide novel data assessing the relationship between cIMT and anxiety in a community-based sample. We found an important moderating effect of gender in the association between the HADS anxiety score and cIMT. The HADS anxiety score was significantly associated with cIMT in men, whereas no association was found among women. The HADS score was second only to age as a predictor of cIMT among men in this population and was a stronger predictor than SBP or the presence of diabetes mellitus among men.

Previous studies have shown that cIMT represents a highly valuable surrogate marker for subclinical atherosclerosis and the risk of cardiovascular events,[11,12] making it a useful epidemiologic tool, particularly in populations in which prospective data are not available, as is the case with South American populations to date. Our study presents, for the first time, evidence of an independent and important association between anxiety and subclinical carotid atherosclerosis in Andean Hispanic adults. Pending prospective data from other Hispanic populations, our findings suggest that anxiety may be associated with an increased cardiovascular risk in Andean Hispanic men. The association between cIMT and the HADS score was independent of age, education, employment status, SBP, DBP, LDL-cholesterol, current smoking, impaired fasting glucose and diabetes mellitus.

The association between subclinical atherosclerosis and anxiety has been previously examined yielding conflicting results.[9,22–29] In line with our findings, Paterniti and colleagues found sustained anxiety predicted 4-year increase of common cIMT.[28] Studies reporting negative associations between anxiety and subclinical atherosclerosis have used different markers of subclinical atherosclerosis such as coronary calcification,[9,29] have been conducted in samples of women only,[24,26,27] or have not assessed for gender moderation.[23,25] Other potential factors explaining the differences in the results may include the questionnaire used to assess anxiety and the characteristics of the study populations. Whereas MESA included U.S. Hispanics, this population may be culturally and genetically different from our population of Andean Hispanics.[22] Alternatively, differences in the measure used to assess anxiety could explain the conflicting results. O'Maley et al. and the MESA investigators used a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Spielberger trait anxiety scale respectively, whereas our study used the anxiety score of the HADS. It is possible that the HADS score performs better as a tool to detect anxiety as it relates to atherosclerotic risk. However, the relative performance of various tools as predictors of subclinical atherosclerosis and cardiovascular risk should be the subject of future studies.

The mechanisms relating anxiety to atherosclerosis are likely to be multiple. Psychosocial factors may be related to atherosclerosis through their association with behavioral risk factors, such as smoking, physical activity, and diet. In our study population, the association between cIMT and the HADS anxiety score among men was independent of smoking status, physical activity (assessed with the International Physical Activity Questionnaire) and consumption of a high-fat diet (data not shown). In addition, anxiety may also promote atherosclerosis through several biologic pathways, including, sympathetic activation,[30,31] subclinical inflammation,[5,32,33] pro-coagulant factors,[34] platelet activation, elevated blood pressure and endothelial dysfunction.[5–7,35] Whereas studies demonstrating the association between these pro-atherogenic factors and anxiety have been performed, further research should be done to establish which of these is more directly responsible for the association between anxiety and subclinical atherosclerosis at the population level. We believe that cIMT will be a useful tool to assess these issues in future research.

We found an independent association between cIMT and anxiety in men but not in women. This gender difference may be due to several potential reasons. First, it is possible that the HADS questionnaire performs differently between men and women. However, this is unlikely given that this questionnaire has been validated in both genders and appeared to perform equally well in men and women.[18] Estrogens may exert a protective effect from potential

pro-atherogenic effects of anxiety. It is possible that differential associations exist in men and women between anxiety and pro-atherogenic abnormalities such as sympathetic activation, subclinical inflammation, pro-coagulant states and/or elevated blood pressure. Finally, it is possible that anxiety has different psychosocial determinants between men and women and that these determinants, rather than anxiety itself, are directly associated with atherosclerosis. These aspects should be the focus of further research.

Further research is also required to assess whether anxiety has a closer association with cIMT versus coronary calcium in men. This will require measurement of both markers in the same individuals. Studies will be also needed to prospectively assess the association between anxiety and progression of subclinical atherosclerosis and to determine whether interventions aimed at decreasing anxiety levels may decrease cardiovascular risk in Hispanic men.

An important strength of our study includes our unselected, community-based sample, which minimizes selection bias. Our study is limited by its moderate sample size and its cross-sectional nature. However, pending prospective data, our findings provide insights into the association between anxiety and subclinical vascular disease in this population.

Conclusions

We found an important moderating effect of gender in the relationship between anxiety and subclinical atherosclerosis. Anxiety was independently associated with subclinical atherosclerosis among Andean Hispanic men, whereas no relationship was found among women. This relationship is independent of classical risk factors. Further studies are required to assess the mechanistic determinants of this association and assess whether interventions to decrease anxiety levels retard the progression of early, subclinical atherosclerosis.

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Conflict of interest statement

The authors have no conflict of interest to disclose.

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