






## ORIGINAL PAPER

# Low levels of awareness, treatment, and control of hypertension in Andean communities of Ecuador

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## Abstract

The major burden of hypertension (HTN) occurs in low-middle-income countries (LMIC) and it is the main modifiable risk factor for cardiovascular diseases (CVD). Few population studies on HTN prevalence have been carried out in Ecuador where there is limited information regarding its prevalence, awareness, treatment, and control. Thus, the aim of the present study was to determine the prevalence, awareness, treatment, and control of HTN and its association with socio-economic, nutritional, and lifestyle habits in urban and rural Andean communities of Pichincha province in Ecuador. The authors studied 2020 individuals aged 35-70 years (mean age 50.8 years, 72% women), included in the Ecuadorian cohort of the Prospective Urban and Rural Epidemiology (PURE) study, from February to December 2018. The hypertension prevalence (>140/90 mmHg) was 27% and was greater in urban than in rural communities, more common in men, in individuals older than 50 years of age, in people with low monthly income and low level of education. Higher prevalence was also observed in subjects with obesity, and among former smokers and those who consumed alcohol. Only 49% of those with HTN were aware of their condition, 40% were using antihypertensive medications, and 19% had their blood pressure under control (<140/90 mmHg). These results showed low levels of awareness, treatment, and control of HTN in the Andean region of Ecuador, suggesting the urgent necessity of implementing programs to improve the diagnosis and management of HTN.

## 1 | INTRODUCTION

Cardiovascular diseases (CVD) are the principal cause of mortality in low-medium-income countries (LMIC).<sup>1</sup> Globally, hypertension (HTN) is the main modifiable risk factor for CVD with a population attributable risk of 32.5% (42.7% for coronary heart disease, 38.9% for stroke, and 21.9% for heart failure).<sup>2</sup> Currently, HTN is common in LMIC where the percentages of awareness, treatment, and control of the disease are very low,<sup>3</sup> particularly in Latin America.<sup>4</sup> Few population studies on HTN prevalence have been carried out in Ecuador, and however, it is not known the rates of awareness, treatment, and control of HTA.<sup>5</sup> Thus, the aim of the present study was to determine the prevalence,

awareness, treatment, and control of HTA and the association with socio-economic, nutritional, and lifestyle habits in urban and rural communities of Pichincha province in Ecuador, that are included in the Prospective Urban and Rural Epidemiology (PURE) study.<sup>4</sup>

## 2 | METHODS

### 2.1 | Study design and participants

Ecuadorian participants (n = 2020) are part of the international cohort of the PURE study, coordinated by the Population Health

Research Institute (Hamilton, Ontario, Canada). The design and methodology of the PURE study have been previously published.<sup>4</sup> Volunteers were recruited from four rural ( $n = 836$ ) and five urban ( $n = 1184$ ) communities of the Pichincha province of Ecuador, located in the Andean mountains with a mean altitude of 2.800 mts above sea level. Pichincha province represents approximately 18% of the Ecuadorian population.<sup>6,7</sup> A multi-stage convenience sample was used to define the study population. Initially, we selected the Pichincha province due to the convenience of logistics and facilities to carry out the recruitment and because it is the second largest province of the country. To select urban communities, we used a list from the Metropolitan District of Quito, the capital city of Ecuador,<sup>7</sup> and to select rural communities, we used the criteria previously defined in the PURE study.<sup>4</sup> Each selected community was defined as a geographical area inhabited with individuals with similar ethnic and cultural characteristics. In order to efficiently recruit participants within each community, we approached suitable public and private institutions willing to participate in the study. From a total of twelve communities, five urban and four rural were selected based on the number of total inhabitants (maximum 5000 in rural areas) and the capability to recruit at least 150 volunteers between 35 and 70 years of age. In order to select the household unit, two strategies were used: (a) Based on local maps close to the recruitment sites, subjects from households were personally invited to participate and (b) word of mouth invitations.

## 2.2 | Survey completion and measurements

Sociodemographic characteristics, anthropometric measurements, and medical history were collected according to the PURE protocol.<sup>1-4</sup> Standardized PURE questionnaires were used to collect sociodemographic characteristics, volunteer's medical history, and risk factors. The variable of education was categorized by years of scholarship as none/primary (0-6 years), high school/secondary (>6-12 years), and university/technical school (>12 years). Household income was divided in tertiles as low (<387 USD/month), medium (387-699 USD/month), and high ( $\geq 700$  USD/month).

A smoker was defined as a participant who had smoked at least one tobacco product daily in the previous 12 months and included those who had quit within the past year. Drinking alcohol was defined as former and current alcohol user (a "yes" response and a "no" if alcohol was never consumed). Blood pressure (BP) was measured using a calibrated automatic digital device (Omron HEM-RML31; Omron Healthcare Co. Ltd., Scarborough, Ontario, Canada) by trained personnel. Previous the measurement, participants sat down for at least 5 minutes; patients were instructed not to eat, smoke cigarettes, or do physical activity (ie, claim stairs), 30 minutes prior to BP measurements. To measure BP, sitting volunteers in upright position had their supported right arm at heart level; brachial artery was located and both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken twice with a time period of 3 minutes

between each measurement; appropriate cuff sizes were used based on individual's phenotype. The average of measurements was used for analysis.

Hypertension was defined with at least one of the following conditions: use of antihypertensive medication or a measured BP with mean of SBP  $\geq 140$  mmHg and/or a mean of DBP  $\geq 90$  mmHg. Awareness of HTN was documented if volunteers reported a previous diagnosis of the condition by a physician. Treated HTN was regarded as the proportion of patients with the condition who received antihypertensive medications. Controlled HTN was defined as the proportion of hypertensive patients with a mean SBP < 140 mmHg and a mean DBP < 90 mmHg, who were taking antihypertensive medication.

Weight and body composition were measured by trained personal with a calibrated scale (Body Composition Monitor, Tanita BC554, Tanita Corporation). Overweight was diagnosed with a BMI  $\geq 25$  and < 30, obesity with a BMI  $\geq 30$ ; abdominal obesity was determined with waist/hip ratio (WHR) in men 0.90 and in women 0.85. For height measurements, a stadiometer was mounted vertically above a hard, flat surface, following vendor instructions (H.A. Kidd & Company, 3021060B); height was measured to the nearest 0.1 cm; waist and hip circumferences were measured using a not expandable tape (VWR International, WLS3678-DD). During anthropometric measurements, volunteers had minimal clothing without shoes.

## 2.3 | Ethics

The Ethics Committee of Universidad San Francisco de Quito approved the study (Code number: 2017-074E). Selected volunteers that signed a written informed consent were included in the study.

## 2.4 | Statistical analyses

Confidence intervals were computed using Wilson score intervals and the differences between rows were analyzed using chi-squared tests. We used log-link Poisson general linear models to evaluate the unconditional estimates and to explore the interactions between several variables. The confidence intervals for the crude prevalence ratios are computed using a Wald-type test. All the functions used in the analyses were implemented in the statistical analysis software R core team version 3.6.0 (2020). A  $P$ -value < .05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Characteristics of study population and prevalence of hypertension

Two thousand and twenty individuals from four rural ( $n = 836$ ) and five urban ( $n = 1184$ ) communities were included in the study. Table 1

Variables	n	HTN Prevalence (%)	[95% CI]	P-value
<b>Sex</b>				
Male	562	36%	[32, 40]	Reference
Female	1458	24%	[21, 26]	<.001
<b>Age group</b>				
≤50	985	14%	[12, 16]	Reference
>50	1035	40%	[37, 43]	<.001
<b>Education level</b>				
None, primary	1001	30%	[28, 33]	Reference
High school/ secondary	671	25%	[22, 29]	.038
University/trade school	348	21%	[17, 26]	<.001
<b>Monthly income (tertiles)</b>				
Low (USD < 387)	665	29%	[26, 33]	Reference
Medium (USD [387, 700])	605	29%	[25, 33]	.878
High (USD > 700)	733	23%	[20, 26]	.008
<b>Residential type</b>				
Rural	836	24%	[21, 27]	Reference
Urban	1184	29%	[27, 32]	.015
<b>Smoking habit</b>				
Never	1641	26%	[23, 28]	Reference
Yes	115	25%	[18, 34]	1
Former	264	38%	[32, 43]	<.001
<b>Drinking alcohol habit</b>				
Never	1433	26%	[24, 28]	Reference
Yes	282	24%	[19, 29]	.484
Former	304	35%	[30, 41]	.001
<b>BMI</b>				
<20	6	17%	[1, 56]	-
[20, 25]	431	18%	[15, 22]	Reference
[25, 30]	907	25%	[23, 28]	.003
≥30	675	35%	[32, 39]	<.001
<b>Abdominal obesity (WHR)</b>				
No	630	18%	[15, 21]	Reference
Yes	1390	31%	[29, 34]	<.001

**TABLE 1** Sociodemographic, habits, and anthropometric characteristics of the study population

Abbreviations: BMI, body mass index; HTN, hypertension

shows the characteristics of the study population. Most participants were women, older than 50 years of age, with non-or primary education, and low income; the mean age of the study population was  $51.4 \pm 9.8$  years. Approximately 59% of the volunteers had urban residency. The majority of participants reported that they had never smoked or consumed alcohol. There were 45% subjects who were overweight, 33% with obesity; and 69% had abdominal obesity. Only 21% of individuals had normal values for BMI.

In the rural area, mean SBP and DBP were  $123.25 \pm 18.55$  and  $77.57 \pm 10.74$ , respectively; and in the urban area, mean SBP and

DBP were  $121.68 \pm 17.51$  and  $79.72 \pm 10.38$ , respectively. The overall prevalence of hypertension was 27% with a 95% CI [25, 29]. Twenty-four percent ( $n = 202$ ; 95%CI [21, 27]) of individuals with HTN lived in the rural area while 29% ( $n = 345$ ; 95%CI [27, 32]) in the urban area. The prevalence of HTN in the rural area ranged from 20% in Guangopolo to 28% in Cuendina, while in the urban area went from 27% in Alangasí and Iñaquito to 37% in Calderón. Hypertension was more common among individuals older than 50 years of age, those with low education level, low monthly income, obesity, and in individuals who reported previous use of cigarettes and alcohol

(Table 1). In addition, there was a significantly higher prevalence of HTN in urban than in rural communities.

The estimated adjusted prevalence ratio (PR) of HTN for age, sex, level of education, income, unhealthy habits, and obesity showed that the disease was 0.59 [0.47, 0.74] less frequent in women than in men and was 2.65 more frequent in subjects older than 50 years of age [2.17, 3.25]. Hypertension was 1.25 [1.04, 1.51] more frequent in individuals that lived in urban compared to those that lived in rural areas; it was more frequent in subjects with obesity than in normal weight individuals (Table 2).

### 3.2 | Prevalence of awareness, treatment, and control of hypertension

The prevalence of HTN awareness was 49%; women and individuals older than 50 years of age were statistically significantly more aware (Table 3). Hypertension awareness was not influenced by education level, monthly income, or residency. Out of the total subjects with hypertension, 40% were receiving treatment at the time of the survey, and women and subjects older than 50 years were more frequently treated.

**TABLE 2** Prevalence ratios by sociodemographic and anthropometric characteristics of the study population

Variables	PR	[95% CI]	P-value	PR*	[95% CI]*	P-value*
Sex						
Male	Reference			Reference		
Female	0.65	[0.56, 0.75]	<.001	0.59	[0.47, 0.74]	<.001
Age group						
≤ 0	Reference			Reference		
>50	2.9	[2.44, 3.45]	<.001	2.65	[2.17, 3.25]	<.001
Education level						
None, Primary	Reference			Reference		
High School/secondary	0.84	[0.72, 0.99]	.035	1.04	[0.84, 1.27]	.721
University/trade School	0.69	[0.55, 0.87]	.001	0.88	[0.65, 1.18]	.397
Monthly income (tertiles)						
Low (USD < 387)	Reference			Reference		
Medium (USD [387, 700])	0.98	[0.83, 1.17]	.853	0.99	[0.81, 1.22]	.952
High (USD > 700)	0.78	[0.66, 0.93]	.007	0.84	[0.66, 1.06]	.142
Residential type						
Rural	Reference			Reference		
Urban	1.2	[1.04, 1.40]	.015	1.25	[1.04, 1.51]	.017
Smoker						
Never	Reference			Reference		
Former	1.47	[1.23, 1.75]	<.001	1.22	[0.95, 1.56]	.121
Yes	0.99	[0.71, 1.37]	1	0.96	[0.64, 1.41]	.852
Alcohol						
Never	Reference			Reference		
Former	1.36	[1.14, 1.62]	.001	0.95	[0.74, 1.22]	.698
Yes	0.92	[0.73, 1.15]	.456	0.84	[0.62, 1.12]	.241
BMI						
<20	-			-		
[20, 25]	Reference			Reference		
[25, 30]	1.42	[1.13, 1.79]	.002	1.31	[1.01, 1.73]	.046
≥30	1.97	[1.57, 2.47]	<.001	1.93	[1.48, 2.56]	<.001
Abdominal Obesity (WHR)						
No	Reference			Reference		
Yes	1.72	[1.43, 2.07]	<.001	1.17	[0.94, 1.47]	.169

Abbreviations: BMI, body mass index; CI, confidence interval; Crude PR, prevalence ratio; PR\*, adjusted prevalence ratios.

**TABLE 3** Prevalence of awareness, treatment, and control by sociodemographic characteristics

Variables	HTN n	Aware% (n)	[95% CI]	Treated % (n)	[95% CI]	Controlled % (n)	[95% CI]
Sex							
Male	203	39 (80)	[33, 46]	31 (62)	[25, 37]	15 (31)	[11, 21]
Female	344	55 (190)	[50, 60]	46 (158)	[41, 51]	22 (74)	[17, 26]
Age group							
<50	135	33 (44)	[21, 41]	27 (37)	[21, 35]	13 (18)	[9, 20]
≥50	412	55 (226)	[50, 60]	44 (183)	[40, 49]	21 (87)	[17, 25]
Education level							
None, Primary	303	51 (154)	[45, 56]	39 (118)	[34, 45]	17 (51)	[13, 21]
High School/ Secondary	171	47 (80)	[39, 54]	42 (71)	[34, 49]	22 (37)	[16, 28]
University/trade school	73	49 (36)	[38, 61]	42 (31)	[32, 54]	23 (17)	[15, 34]
Monthly income (tertiles)							
Low (USD < 387)	196	49 (96)	[42, 56]	37 (73)	[31, 44]	15 (30)	[11, 21]
Medium (USD [387, 700])	175	46 (81)	[39, 54]	37 (64)	[30, 44]	18 (32)	[13, 25]
High (USD > 700)	169	53 (89)	[45, 60]	47 (79)	[39, 54]	24 (41)	[18, 31]
Residential type							
Rural	202	46 (92)	[39, 52]	35 (70)	[28, 41]	15 (30)	[11, 20]
Urban	345	52 (178)	[46, 57]	43 (150)	[38, 49]	22 (75)	[18, 26]
Smoker							
Never	419	53 (220)	[48, 57]	42 (177)	[38, 47]	19 (80)	[16, 23]
Former	99	41 (41)	[32, 51]	35 (35)	[27, 45]	22 (22)	[15, 31]
Yes	9	31 (9)	[17, 49]	28 (8)	[15, 46]	10 (3)	[4, 26]
BMI							
[20, 25]	77	44 (34)	[34, 55]	32 (25)	[23, 44]	17 (13)	[10, 27]
[25, 30]	230	43 (100)	[37, 50]	35 (81)	[29, 42]	17 (40)	[13, 23]
>30	238	57 (135)	[50, 63]	47 (113)	[41, 54]	22 (52)	[17, 28]

Abbreviations: BMI, body mass index; HTN, hypertension.

There was no association between individuals with hypertension that were under treatment and their level of education, monthly income, and residency. Moreover, only 19% of all subjects with hypertension had their levels of blood pressure well controlled, with a trend favoring women more controlled than men. Hypertension control was not influenced by sex, age, level of education, monthly income, or obesity. From all of subjects knowledgeable of their disease, 79% (n = 214) were under pharmacologic treatment, but only 48% of those receiving medications (n = 105) were well controlled.

### 3.3 | Factors that affect the level of hypertension awareness

There was significantly more awareness of HTN among women and individuals older than 50 years of age. In addition, subjects with obesity were more aware than those with overweight (Table 3). On

the other hand, awareness of HTN was not influenced by education level, monthly income, residency (urban or rural), and the habit of smoking or drinking.

### 3.4 | Factors that affect the level of hypertension treatment and control

Older individuals and women had greater percentage of treatment than subjects younger than 50 years of age and men. Other variables including education level, monthly income, residency (urban or rural), the habit of smoking, and BMI did not affect the percentage of individuals that received antihypertensive treatment (Table 3). There were not differences in the level of hypertension control among individuals regardless of their age group and sex. A similar pattern of hypertension control was observed when we considered the education level, monthly income, residency (urban or rural), the habit of smoking and drinking, and BMI.

## 4 | DISCUSSION

Present results indicate that hypertension prevalence is an important public health problem in both urban and rural Andean communities in Ecuador. The frequency of HTN was more common in men older than 50 years of age, in individuals with low income, low level of education and that lived in the urban area. Higher prevalence was also observed in subjects with obesity and among those that used to smoke and consumed alcohol. Approximately half of our population who had HTN were aware of their condition; 40% of them were under pharmacologic treatment; and only 19% of individuals with hypertension had their BP under control.

Prevalence of hypertension in the present study is much higher than the reported in 2012 for the similar age group; however, direct comparison cannot be established due to different methodologies used in both studies.<sup>5</sup> Regardless of this, our results suggest that HTN is an increasing health problem in Ecuador. Differently to other reports, present results showed higher prevalence of hypertension in urban communities compared to the rural ones.<sup>3,4</sup> The rural parish of Guangopolo had significant lower prevalence of HTN compared with the other rural communities. Among urban communities, Calderón had the highest prevalence of HTN. This county is one of the fastest growing settlements in the periphery of Quito, with limited public health services.<sup>8</sup> These results indicate that there is heterogeneity in the prevalence of HTN within urban and rural communities.

Our results in the Andean communities of Ecuador showed that the prevalence of HTN (27%) is lower in relation to the observed in the other Latin American countries that are part of the PURE cohort<sup>4</sup> such as Brazil (52.5%), Argentina (49.5%), Chile (45.5%), and Colombia (37.5%; Table 4). The present analysis does not permit to determinate the reason for these differences, but it is possible that it could be related to socio-economic conditions or to ethnic differences existing between these countries.<sup>4</sup> In the Andean communities included in the present study, several well-known risk factors are associated with a high prevalence of HTN as older age, quit smoking, low income, low education, overweight, and obesity.<sup>9</sup> With the exception of one community, all were located over 2,400 meters over sea level. Hypoxia of high altitude is considered a risk factor for HTN, although there is controversy about this issue.<sup>10,11</sup> In Colombian and Peruvian cohorts, individuals living at altitudes higher than 2,000 meters above sea level had lower frequency of hypertension in relation to individuals living at low altitude.<sup>12,13</sup> In Colombia, the prevalence of HTN in individuals participating of the PURE study was 36.0%

in the altitude communities while at sea level was 44.8%.<sup>12</sup> Except for Pacto, all our studied communities are located at altitudes higher than 2,400 meters above sea level opening the possibility that the altitude could explain partially the lower prevalence of HTA observed in our Andean communities in relation to the reported in Colombia. However, the association between HTN and altitude is not clear. Further studies are needed.

The levels of awareness of hypertension observed in the present study were similar with those reported in other Latin American countries participating of the PURE study, being higher in the urban communities (Table 4).<sup>4,12</sup> The higher knowledge of HTN in urban settings could be related to higher levels of education and income, and also by an increased access to health care systems.<sup>12</sup> These results are of concern, since almost half of the population with HTN in this region do not know that they suffer of this mayor preventable and treatable risk factor for CVD. In a recent report from the prospective Italian study, the Brisighella Heart Study (BHS), the awareness of hypertension among 1652 individuals without atherosclerotic cardiovascular disease was approximately 24% that is lower than the level of awareness in the current study. It is possible that the lower level of awareness could be explained by the absence of atherosclerotic cardiovascular disease in the BHS. In that study, 19.5% and 22.5% individuals had abnormal high serum values of cholesterol and triglycerides without their awareness.<sup>14</sup> The authors concluded that the lack of awareness of hypercholesterolemia and hypertension is frequent and it is associated with higher arterial stiffness. It will be important to determine the level of awareness of dyslipidemia in the general population since this is a common modifiable risk factor associated with CVDs.<sup>14</sup> In general, to increase the awareness of HTN and other modifiable risk factors, it will be important to improve the levels of education, income, and health care, including ample screening programs, particularly in the rural areas.

In the present study, 40% of individuals with hypertension were receiving antihypertensive treatment, but this increased to 79% in those patients that were aware of their condition, a situation that is similar than the one observed in other PURE Latin American countries (Table 4).<sup>4</sup> A comparison of the situation in the present study from Ecuador, with the report of the other countries in Latin America that participate of the PURE study, demonstrates that the percentage of individuals with hypertension that received treatment is lower (40% versus 53%). Moreover, in the other Latin American countries, almost 91% of individuals mindful of their HTN are under

**TABLE 4** Comparison of the prevalence, awareness, treatment, and control of hypertension in Pichincha province of Ecuador and other Latin American studies

Study	HTN prevalence			Treated overall %	Controlled overall %	Aware %	Treated and aware	Treated and controlled	Refs.
	Urban	Rural	Total						
Latin- America	44.8	42.1	44	53.3	20.1	59	90.5	37.6	<sup>5</sup>
Colombia	30	35.9	37.5	46	17.3	51.9	77.5	37.1	<sup>6</sup>
Pichincha province	29	24	27	40	19	49	79	48	Present study

Abbreviation: HTN, hypertension.

treatment while in the present study only 79%. Overall, it is evident that it is necessary not only improve the awareness but also the rates of treatment of HTN. Our data indicate that only 19% of all individuals with HTN had their BP under control, and approximately 48% of those individuals with pharmacologic antihypertensive therapy (Table 4). The percentage of individuals with controlled HTN in this study is similar to other Latin American countries. Moreover, when we compared the percentage of individuals under pharmacologic treatment with controlled BP (48%) in the present study was lower than the one observed in Peru (62%).<sup>13</sup> Thus, our results indicate that in Ecuador, despite the lower prevalence of HTN, the levels of awareness and treatment are poorer than in other Latin American; nevertheless, individuals that received antihypertensive therapy presented better control than those treated in other Latin American countries (Table 4). The small percentage of adequate control among all the hypertensive individuals and in those that receive treatment could be due to the small proportion of individuals aware of their disease and inadequate treatment, lack of compliance and interest to receive it; also, other factors such as access to the health care system, availability, and the affordability of antihypertensive medication depend on the socio-economic conditions of the individual and the public health care system.<sup>12</sup> Also, the Ecuadorian public health care system has not adopted combined antihypertensive therapies that have shown better control and compliance.<sup>15</sup> These factors should be considered in planning any intervention program.

Several factors were identified as modulators of HTN awareness, treatment, and control that need to be considered in order to decrease the burden of the disease. For instance, individuals older than 50 years of age were more aware, more frequently received treatment and had better control of the disease than younger individuals; these patterns were also observed in subjects that never smoked with high income and with obesity.

These data indicate that particular targets to educate and prevent the disease include young male smoker subjects with low income. Currently, there are national and international interventions aimed to improve the diagnosis and management of HTN. For instance, Ecuador is implementing the May Month of Measurement (MMM) initiative,<sup>16</sup> with the support of the International Society of Hypertension, World Health Organization (WHO)/Pan American Health Organization and the Ministry of Public Health. Similarly, another example is the implementation of the HEARTS initiative, recommended by WHO, which includes a standardized clinical training program with certification for blood pressure measurement, routine screening for hypertension in clinics and in the community, a simple pharmacologic treatment algorithm, and a registry with performance reporting and feedback.<sup>17</sup>

We acknowledge some limitations in the present study including the local nature of the data that does not represent the country, the study was carried out in one of the largest province of Ecuador; a convenience sample was done following the PURE methodology that could differ if a probabilistic sample would have been used that could have yielded a similar proportion of participating males and females; also, data on awareness and treatment of HTN was obtained

by direct interview with the participants and it is possible that data are not completely accurate.

Present study expands the knowledge and complexity of HTN in the Andean region and Latin America. Results indicated that there are particularities in the prevalence, awareness, treatment, and control of the disease that need to be considered at the local level to implement appropriate measures to manage this important health problem. Thus, this cohort from Ecuador presents a relative low prevalence of HTN. However, we also observed lower levels of awareness, treatment, and control than the ones reported for other Latin American countries. Programs aimed to control the disease should put special emphasis in the population at highest risk including younger men and smokers.

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#### CONFLICT OF INTEREST

All authors indicate that they do not have conflict of interest in the present manuscript.

#### AUTHOR CONTRIBUTIONS

Felix C conceived study, interpreted data, reviewed manuscript, and obtained funding. Baldeon ME conceived study, analyzed and interpreted data, wrote manuscript, and coordinated submission. Zertuche F conducted statistical analysis and interpreted data, reviewed manuscript. Fornasini M conceived study, analyzed and interpreted data, wrote manuscript, and coordinated submission. Paucar MJ contributed to the design of the study, data collection, and provided critical review of the manuscript. Ponce L contributed to the design of the study, data collection, and provided critical review of the manuscript. Rangarajan S conceived study, interpreted data, and reviewed manuscript. Yusuf S conceived study, obtained funding, interpreted data, and reviewed manuscript. López-Jaramillo J conceived study, obtained funding, analyzed and interpreted data, and reviewed manuscript.

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