

## ORIGINAL ARTICLE

## Prevalence of Peripheral Artery Disease and Associated Risk Factors in a Brazilian Rural Population: The Baependi Heart Study

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### Abstract

**Background:** The identification of peripheral artery disease (PAD) can help prevent further progression of the disease and additional complications, considering that this condition is a risk factor for all-cause mortality and cardiovascular death.

**Objective:** To assess the prevalence of PAD in the Baependi Heart Study and investigate associated risk factors in different age groups.

**Methods:** A total of 1,627 individuals (of both genders and aged 18 - 102 years) residing in the municipality of Baependi (Minas Gerais, Brazil) were selected for this study. Anthropometric and biochemical parameters were evaluated by standard techniques. Physical activity level was determined by the International Physical Activity Questionnaire - Short Form (IPAQ-SF). The screening of PAD was performed by determination of the ankle-brachial index (ABI). The level of statistical significance was set at 5%.

**Results:** In the overall sample, the prevalence of PAD was 1.05%, and reached 5.2% after the age of 70 years. The frequency and intensity of smoking were higher in individuals with PAD. A prior history of myocardial infarction and a higher prevalence of hypertension, diabetes, obesity, and sedentary lifestyle were also associated with PAD. In addition, PAD was more frequent in blacks than whites. In multivariable analysis, age, diabetes, smoking, and physical inactivity remained independently associated with PAD.

**Conclusion:** The prevalence of PAD was low and increased clearly with age in our sample from a Brazilian rural population. Furthermore, the main risk factors for PAD in the investigated sample were smoking, sedentary lifestyle, diabetes mellitus, and age. (Int J Cardiovasc Sci. 2018; [online].ahead print, PP.0-0)

**Keywords:** Peripheral Arterial Disease / prevalence; Risk Factors; Rural Population; Tobacco Use Disorder; Ankle-Brachial Index.

### Introduction

Peripheral artery disease (PAD) is classically defined as a condition affecting noncardiac, nonintracranial arteries, majorly due to atherosclerosis, that leads to partial obstruction of the peripheral arteries, reducing perfusion to the tissues irrigated by these arteries.<sup>1,2</sup> Even though PAD is asymptomatic in most patients, the disease may progress with clinical symptoms (like

claudication) and eventually lead to tissue necrosis. The identification of PAD can help prevent further progression of the disease itself and additional complications, considering that this condition is a risk factor for all-cause mortality<sup>3-8</sup> and cardiovascular death,<sup>3,4,7,9</sup> including coronary artery disease<sup>3,7</sup> and stroke.<sup>5,7</sup> PAD is also a major cause of quality of life impairment, which in turn, worsen even more with the progression of the disease.<sup>10,11</sup> Therefore, information

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DOI: xx.xxxx/xxxx-xxxx.xxxxxxxx

Manuscript received July 26, 2016, revised manuscript September 28, 2017, accepted October 15, 2017.

on the prevalence of PAD is important to allow proper planning in public health care. Recommendations on the identification and management of this condition have been published by international medical societies.<sup>12-14</sup>

Epidemiological studies have determined that the prevalence of PAD in the general population range from 4-10%;<sup>15-23</sup> however, there is a clear increase in prevalence with increasing age,<sup>13,17,19,24</sup> with rates as high as 20% over the age of 70 years.<sup>19,20</sup> Data on the prevalence of PAD in the general Brazilian population are scarce. Only one large multicenter study assessed the prevalence of PAD and found a high rate (10.5%) in 1,159 individuals in the general population.<sup>18</sup> Other studies have investigated the prevalence of PAD specifically in Japanese-Brazilians<sup>25,26</sup> and in a small sample of patients with diabetes.<sup>27</sup> Therefore, other large studies are needed to better assess the prevalence of PAD and understand the risk factors associated with this condition in the general Brazilian population.

The Baependi Heart Study is an ongoing Brazilian cohort study established in 2005 to investigate cardiovascular risk factors and heritability.<sup>28</sup> The study has now expanded to include other investigations such as nocturnal polygraph, heart rate variability, pulse-wave velocity, 24-hour ambulatory blood pressure monitoring, 24-hour electrocardiography (Holter), and assessment of vascular age by plethysmography. Using data collected from 2010 to 2013 from the above-mentioned research project, the present study aimed to assess the prevalence of PAD and investigate associated risk factors in different age groups.

## Methods

### Study sample

The Baependi Heart Study is a genetic epidemiological study of cardiovascular disease risk factors with a longitudinal design, whose methodology has been previously described.<sup>28</sup> For the present analysis, we carried out a cross-sectional evaluation of data collected in the second visit of the protocol (between 2010 and 2013). This study invited 2,072 individuals (of both genders and aged 18 - 102 years), distributed across 109 families residing in the municipality of Baependi, a city in a rural area (752 km<sup>2</sup>, 18,072 inhabitants) located in Minas Gerais State, Southeast of Brazil. Of these, 1,634 participants underwent screening for PAD. The study protocol was approved by the ethics committee of the *Hospital das Clínicas* (SDC: 3485/10/074), University of

São Paulo, Brazil. All procedures involved in this study are in accordance with the Declaration of Helsinki from 1975, updated in 2013. Informed consent was obtained from all participants included in the study.

### Anthropometric evaluations

Anthropometric parameters were measured according to a standard protocol.<sup>28</sup> Height was measured in centimeters and weight in kilograms using a calibrated digital balance. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m<sup>2</sup>). Waist circumference was measured at the mean point between the lowest rib margin and the iliac crest with the subject standing and at the maximum point of normal expiration. Obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>.

### Blood pressure measurements

Blood pressure was measured with a standard digital sphygmomanometer (OMRON, OMRON Eletrônica do Brasil Ltda., SP, Brazil) on the left arm after 5 minutes of rest, with the subject in the sitting position. Systolic (SBP) and diastolic blood pressures (DBP) were calculated from three readings (mean value of all measurements), with a minimal interval of 3 minutes.<sup>28</sup> Hypertension was defined as a mean SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg and/or use of antihypertensive drug.<sup>29</sup>

### Biochemical measurements

Blood levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting glucose were measured by standard techniques in 12-h fasting blood samples.<sup>30</sup> Glycated hemoglobin (HbA1c) levels were determined by high-performance liquid chromatography (National Glycohemoglobin Standardization Program, USA). Diabetes mellitus was diagnosed in the presence of a fasting glucose  $\geq 126$  mg/dL, HbA1c  $\geq 6.5\%$ , or use of antidiabetic drugs. *Hypercholesterolemia* was defined as a total cholesterol level  $\geq 240$  mg/dL.

### Assessment of risk factors and depression

Physical activity level was determined by the International Physical Activity Questionnaire - Short Form (IPAQ-SF). Sedentary lifestyle was identified based on a duration of physical activity lower than 10 minutes/day on the previous week.

Information regarding medical history (angina pectoris, myocardial infarction, stroke, kidney failure, and depression) and environmental risk factors such as smoking and alcohol use were evaluated through a questionnaire completed by each participant. The questionnaire was based on the World Health Organization's Multinational Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)<sup>31</sup> project epidemiological instrument, and was applied and filled out by research assistants specifically trained for this task.

### Screening of peripheral artery disease

The screening of PAD was performed with the ankle-brachial index (ABI), which was measured by a single trained examiner using a sphygmomanometer (Heidji, Brazil) with a cuff suitable for the circumference of the limbs and a 10 MHz portable Doppler device (DV 610B, MEDMEGA, SP, Brazil).

The ABI was determined for each leg by the ratio between the highest SBP obtained at the ankle (posterior tibial and dorsalis pedis arteries) and highest SBP obtained in the arms (brachial artery).<sup>12-14</sup> The methodology of the test and the ABI classification were based on recommendations of the American College of Cardiology / American Heart Association (ACC/AHA).<sup>12,13</sup> ABI values between 0.91 and 1.39 were considered normal. Values  $\leq 0.90$  were considered compatible with PAD and values  $\geq 1.40$  were considered inconclusive for PAD and were excluded from the analysis.

### Statistical analysis

Categorical variables were compared using the chi-square test and are presented as percentage, while continuous variables are presented as mean  $\pm$  standard deviation. The normality of the data was confirmed with the Kolmogorov-Smirnov test. Unpaired Student *t* test was performed to analyze demographic, hemodynamic, and biochemical data according to PAD status. Since the cutoff value for PAD diagnosis based on ABI is well-established in the literature, we carried out univariate and multivariate logistic regression analyses to determine the association between PAD (ABI  $< 0.9$ ) as the dependent variable and age, hypertension, diabetes, myocardial infarction, smoking, and sedentary lifestyle as predictor variables. Statistical analyses were carried out using SPSS

(version 19) software (Chicago, IL, USA), with the level of significance set at 5%.

## Results

A total of 1,634 individuals were screened for PAD. Seven individuals presented an ABI above 1.4 and were excluded from the analysis. Therefore, 1,627 volunteers were included in the study. The age of the participants ranged from 18 to 102 years (mean  $44.9 \pm 16.4$  years). Table 1 shows the demographic, anthropometric, biochemical, and hemodynamic characteristics of the individuals with and without PAD, defined as an ABI equal to or lower than 0.9. Age, BMI, HbA1c, and SBP were higher in volunteers with PAD. The presence of PAD was also more frequent in elderly compared with younger individuals, and in blacks compared with whites.

Figure 1 presents the data related to the prevalence of PAD using the ABI in different age groups. Overall, the prevalence was very low (1.05%). Only one case of PAD was observed below the age of 30 years, and the prevalence of PAD increased after the fifth decade, peaking at the age of 70 years, when it reached 5.2%. The frequency of PAD by decade is presented in the Table 2.

Table 3 presents the data related to the lifestyle characteristics of the volunteers. The frequency and amount of smoking were higher in individuals with PAD. There was also a higher frequency of physically inactive volunteers in the PAD group.

Table 4 presents a comparison of clinical characteristics in individuals with and without PAD. A higher prevalence of hypertension, diabetes, and obesity was observed in individuals with a diagnosis of PAD. The presence of hypercholesterolemia was not different between groups. Also, a prior history of myocardial infarction was more frequent in the PAD group.

Table 5 presents univariate and multivariate logistic regression models for PAD. In multivariate analysis, age, diabetes, smoking, and physical inactivity were significantly and independently associated with PAD.

## Discussion

In terms of the number of individuals included, the present study is the largest investigation of the prevalence of PAD in a Brazilian population. The Baependi Heart Study is a Brazilian cohort study investigating cardiovascular risk factors and heritability in residents of

**Table 1 - Demographic, anthropometric, biochemical, and hemodynamic characteristics of individuals with and without peripheral artery disease**

Variables	Total	PAD present	PAD absent	P value
n	1,627	17	1,610	***
Age (years)	44.9 ± 16.4	66 ± 15	45 ± 16	< 0.001
Gender				
Men (%)	41.5	41.2	41.5	0.59
Women (%)	58.5	58.8	58.5	
Ethnicity				
White (%)	76.7	70.6	76.8	0.001
Black (%)	5.5	29.4	5.2	
Mulatto (%)	17.5	0	17.7	
Others (%)	0.3	0	0.4	
ABI (ratio)	1.11 ± 0.1	0.78 ± 0.11	1.12 ± 0.7	< 0.001
BMI (kg/m <sup>2</sup> )	25.8 ± 5.1	28.7 ± 5.3	25.7 ± 5.1	0.02
WC (cm)	91 ± 12	100 ± 10	91 ± 12	0.003
TC (mg/dL)	197.8 ± 40.7	195.6 ± 59.9	197.9 ± 40.5	0.83
LDL-c (mg/dL)	124.5 ± 35.4	122.2 ± 56.3	124.6 ± 35.2	0.79
HDL-c (mg/dL)	47.2 ± 11.7	45.2 ± 13.1	47.2 ± 11.8	0.49
Triglycerides (mg/dL)	130.3 ± 68.1	141.1 ± 60.0	130.2 ± 68.2	0.52
Fasting glucose (mg/dL)	92.6 ± 19.0	114.6 ± 43.2	92.3 ± 18.5	0.06
HbA1c (%)	5.7 ± 0.7	6.5 ± 1.2	5.7 ± 0.8	0.02
SBP (mmHg)	125.4 ± 16.3	133.5 ± 19.2	125.4 ± 16.2	0.04
DBP (mmHg)	76.2 ± 10.3	75.3 ± 9.2	76.2 ± 10.4	0.72

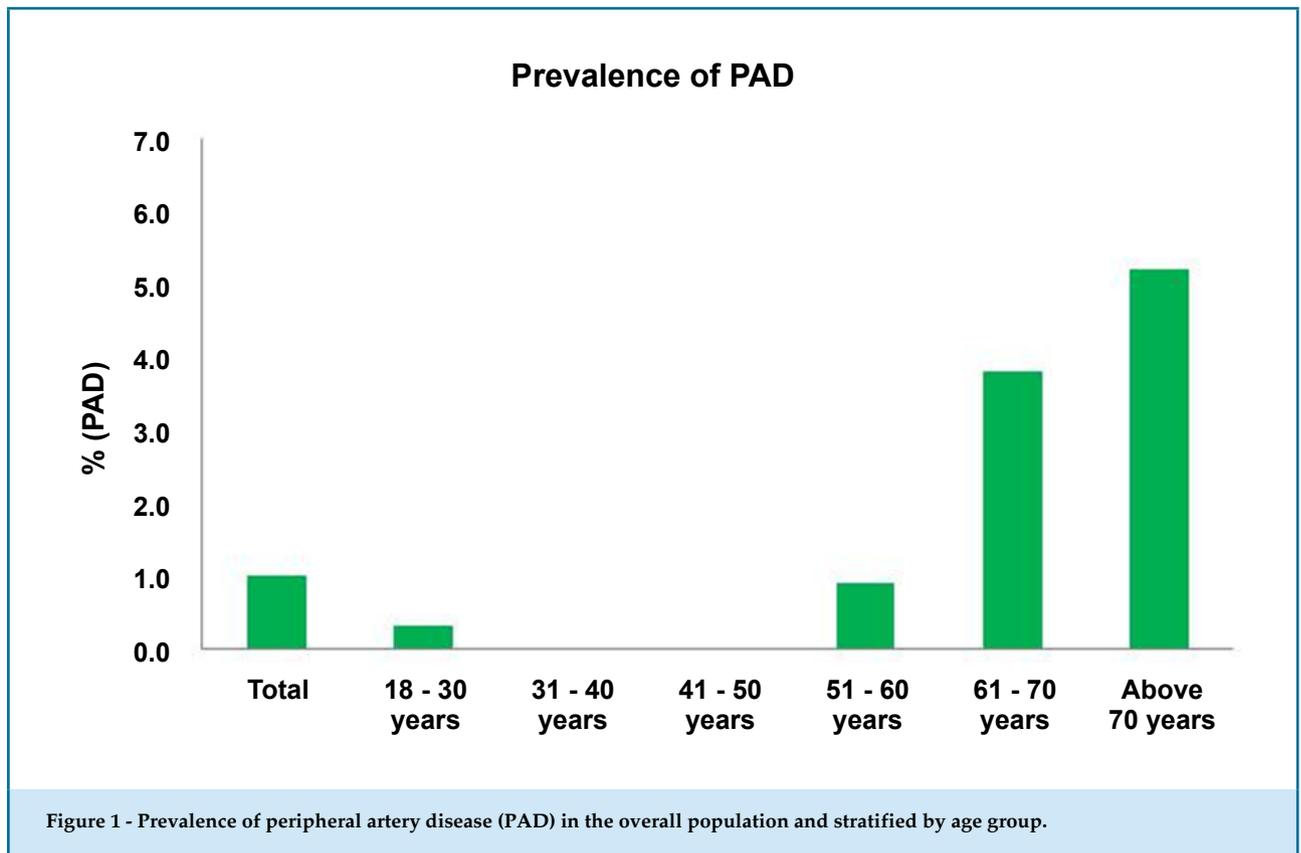
*Categorical variables were compared using the chi-square test, and continuous variables were compared using Student t test. PAD: peripheral artery disease; n: sample size; ABI: ankle-brachial index; BMI: body mass index; WC: waist circumference; TC: total cholesterol; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; HbA1c: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

the rural city of Baependi, located in Southeastern Brazil. In the study sample, which included 1,627 volunteers, the overall prevalence of PAD was 1.05%. The prevalence clearly increased with age, peaking at 5.2% above the age of 70 years. Individuals with PAD were older, heavier, more often smokers, and less physically active. Identified risk factors for PAD in the study sample were age (odds ratio [OR] = 1.08), smoking (OR = 4.01), sedentary lifestyle (OR = 3.75), and diabetes mellitus (OR = 3.07).

The occurrence of PAD in the general population has been assessed in different countries.<sup>15-17,19,20,22,23,32</sup> In Brazil, Makdisse et al.<sup>18</sup> reported in 2008 a high prevalence of PAD (10.5%) in a population with a mean age of 43.8 ±

14.7 years. The study involved volunteers in large cities (over 100 thousand inhabitants) from different Brazilian regions. Another study specifically assessed the Japanese-Brazilian population and determined a prevalence of PAD of 21.1%;<sup>26</sup> however, the mean age of the participants in this study was higher (about 56.5 years). The present study assessed volunteers from a city with an estimated population of 18,072 inhabitants at the time of the study. The prevalence found (around 1%) is considerably low.

Most studies assessing the prevalence of PAD have included samples of individuals older than 40 years (sometimes above the ages of 55 or 65 years). If we consider only the prevalence of PAD in individuals



Age (n)	PAD overall prevalence n cases (%)	PAD prevalence men n cases (%)	PAD prevalence women n cases (%)
Below 30 (397)	1 (0.3)	1 (0.6)	0 (0)
31 - 40 (279)	0 (0)	0 (0)	0 (0)
41 - 50 (335)	0 (0)	0 (0)	0 (0)
51 - 60 (316)	3 (0.9)	1 (0.8)	2 (1.1)
61 - 70 (184)	7 (3.8)	2 (2.5)	5 (4.8)
Above 70 (116)	6 (5.2)	3 (5.4)	3 (5.0)

PAD: peripheral artery disease.

older than 40 years in the present study (1.7%), the data are lower but in agreement to those of other studies such as the ones performed in Sri Lanka by Weragoda et al.<sup>32</sup> in 2015 (3.6%, n = 2,912) and in the

US by Razzouk et al.<sup>22</sup> in 2015 (the Life Line Screening®, 4.1%, n = 3.67 million), and Eraso et al.<sup>16</sup> in 2015 (4.6%, n = 7,058), which identified prevalence rates below 5% in the general population. In a study published in 2016, Alzamora et al.<sup>15</sup> described a prevalence of new PDA of 4.3% (n = 2,256) in a study with a follow-up of 5 years conducted in a Spanish population aged more than 55 years and described as having low-risk factors for cardiovascular disease.

In the present study, the prevalence of PAD above the age of 50 years was 2.6%. As expected, age was independently associated with a diagnosis of PAD, as identified by the present and previous studies. Therefore, the low prevalence of PAD in the present study is partially due to the low mean age of the participants, the inclusion of volunteers with age starting at 18 years, and the fact that most volunteers (62.1%) were below the age of 50 years. Additionally, our sample had only about 7% (n = 116) of the volunteers above the age of 70 years, a group in which a higher prevalence of PAD is expected.<sup>15-17,19,20,32</sup>

Volunteers with PAD in the present study were older and had higher BMI, HbA1c, and SBP levels compared

**Table 3 - Lifestyle characteristics of individuals with and without peripheral artery disease**

Lifestyle characteristics	Total (1,627)	PAD present (n = 17)	PAD absent (n = 1,610)	P value
Smoking				
Have you ever smoked cigarettes?				
Yes, and still smoke	11.0%	5.9%	11.1%	
Yes, in the past	23.3%	58.8%	22.9%	0.02
No	65.7%	35.3%	66.0%	
N° of cigarettes/day	13.3 ± 12.3	23.2 ± 14.3	13.1 ± 12.2	0.007
Alcohol consumption				
Daily	0.9%	0%	0.9%	
1-3 days/ week	10.0%	0%	10.1%	
4-6 days/ week	0.9%	0%	0.9%	
1-3 days/ month	11.0%	5.9%	11.1%	0.70
Less than 1 day/ month	6.0%	11.8%	6.0%	
Gets drunk at least once a month	0.7%	0%	0.7%	
None	70.4%	82.3%	70.3%	
Physical activity				
Very active	3.4%	0%	3.5%	
Active	30.1%	5.9%	30.4%	0.05
Irregularly active	25.2 %	17.6%	25.3%	
Sedentary	41.2%	76.5%	40.8%	

*Alcohol consumption (mean frequency of alcohol intake in the last 12 months); physical activity (activities carried out in the last week - International Physical Activity Questionnaire - Short Form [IPAQ-SF]). All variables are categorical and were compared using chi-square test. PAD: peripheral artery disease.*

with volunteers with normal ABI. Furthermore, a higher prevalence of physical inactivity, obesity and smoking frequency and intensity (cigarettes/day) was found in volunteers with PAD. These variables are frequently associated with PAD in other studies.<sup>15-17,19,20,22,23,32</sup> The present study also identified a higher frequency of PAD in blacks compared with whites. This finding is aligned with recent data published by Eraso et al.,<sup>16</sup> who assessed data from the National Health and Nutrition Examination Survey (NHANES), including 7,058 subjects above the age of 40 years. Another potential explanation for the low prevalence of PAD in the assessed population is the fact that the study was conducted in a small town where overall habits (e.g., nutritional)

and exposure to risk factor (e.g., mental stress), other than the investigated here, are different from those observed in large cities. Comparing our population with the one included in the study by Makdisse et al.<sup>18</sup> (conducted in large Brazilian cities), our results showed a lower percentage of smokers (34.3% versus 46.7%) and physically inactive individuals (41.18% versus 64.8%). Also, the study by Makdisse et al.<sup>18</sup> had a larger number of individuals with chronic kidney disease (2.46% versus 6.12%), which is a well-known risk factor for PAD.<sup>16,33</sup>

Upon applying a multivariable logistic regression model, we determined the independent predictors associated with PAD. Only age, diabetes mellitus, smoking, and sedentary lifestyle emerged as significant

**Table 4 - Comparison of clinical characteristics among individuals with and without peripheral artery disease**

Clinical characteristics	Total (1,627)	PAD present (n = 17)	PAD absent (n = 1,610)	P value
<b>Hypertension (%)</b>				
Yes	40.0	82.4	39.6	< 0.001
No	60.0	17.6	60.4	
<b>Diabetes (%)</b>				
Yes	7.7	41.2	7.4	< 0.001
No	92.3	58.8	92.6	
<b>Obesity (%)</b>				
Yes	19.1	41.2	18.9	0.03
No	80.9	58.8	81.1	
<b>Hypercholesterolemia (%)</b>				
Yes	15.9	12.5	15.9	0.52
No	84.1	87.5	84.1	
<b>Angina pectoris (%)</b>				
Yes	3.0	5.9	2.9	0.40
No	97.0	94.1	97.1	
<b>Myocardial infarction (%)</b>				
Yes	2.2	11.8	2.1	0.05
No	97.8	88.2	97.9	
<b>Stroke (%)</b>				
Yes	0.6	5.9	0.5	0.09
No	99.4	94.1	99.5	
<b>Kidney failure (%)</b>				
Yes	2.5	5.9	2.4	0.35
No	97.5	94.1	97.6	
<b>Depression (%)</b>				
Yes	19.2	29.4	19.1	0.21
No	80.8	70.6	80.9	

All variables are categorical and were compared using the chi-square test. PAD: peripheral artery disease.

risk factors in the study sample. This finding is aligned with that of several other studies.<sup>16,17,19,32,34</sup> Even though PAD is majorly caused by atherosclerotic disease, hypercholesterolemia was not found as a significant risk

**Table 5 - Univariate and multivariate logistic regression analysis of peripheral artery disease (defined as an ankle-brachial index < 0.90) in a Brazilian population**

Variables	PAD	
	OR (95%CI), P value	
	Univariate	Multivariate
Age	1.08 (1.05 to 1.13), < 0.001	1.08 (1.03 to 1.13), 0.001
Hypertension	7.12 (2.04 to 24.90), < 0.001	1.53 (0.39 to 5.98), 0.54
Diabetes	8.77 (3.28 to 23.46), < 0.001	3.07 (1.07 to 8.85), 0.04
Obesity	3.01 (1.14 to 7.96), 0.03	2.89 (0.97 to 8.66), 0.06
Myocardial infarction	6.18 (1.36 to 28.07), 0.02	2.19 (0.44 to 11.02), 0.34
Smoking	3.56 (1.31 to 9.68), 0.01	4.01 (1.34 to 11.97), 0.01
Sedentary lifestyle	4.70 (1.53 to 14.48), 0.007	3.75 (1.16 to 12.03), 0.03

Multivariate model: age, hypertension, diabetes, obesity, myocardial infarction, smoking, and sedentary lifestyle. PAD: peripheral artery disease; OR: odds ratio; 95%CI: 95% confidence interval.

factor. Other studies have also found a weak association between PAD and hypercholesterolemia when comparing risk factors<sup>16</sup> or no association whatsoever.<sup>35</sup>

Our study has some limitations. First, as a cross-sectional analysis, a causal relationship between several cardiovascular risk factors and PAD could not be established. Second, the diagnosis of PAD in the present study was established only by ABI. Despite being a simple and inexpensive method, studies have shown that ABI has a high sensitivity (90 - 97%) and specificity (98 - 100%) for detection of arterial stenosis greater than 50%.<sup>36</sup>

## Conclusion

In summary, in a sample from the Brazilian population, aged 18 years and above and residing in a small rural town, PAD had a low prevalence, clearly increased with age, and was more frequent in blacks than whites. Additionally, risk factors for PAD in the investigated population were smoking, sedentary lifestyle, diabetes mellitus, and age,

which are similar to those in other epidemiological studies including different ethnic groups.

### Author contributions

Conception and design of the research and writing of the manuscript: Alvim RO, Dias FAL, Krieger JE, Pereira AC; Acquisition of data and analysis and interpretation of the data: Alvim RO, Dias FAL, Oliveira CM, Horimoto ARVR, Ulbrich AZ; Statistical analysis: Alvim RO; Obtaining financing: Krieger JE; Critical revision of the manuscript for intellectual content: Oliveira CM, Horimoto ARVR, Ulbrich AZ, Pereira AC.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Sources of Funding

This study was funded by FAPESP, Hospital Samaritano and SUS.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number SDC: 3485/10/074. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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