

ORIGINAL RESEARCH

Prevalence of and Risk Factors for Peripheral Artery Disease in Rural South Africa: A Cross-Sectional Analysis of the HAALSI Cohort

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BACKGROUND: The burden of peripheral artery disease (PAD) is increasing in low- and middle-income countries. Existing literature from sub-Saharan Africa is limited and lacks population-representative estimates. We estimated the burden and risk factor profile of PAD for a rural South African population.

METHODS AND RESULTS: We used data from 1883 participants from a rural, low-income cohort of South African adults aged 40 to 69 years with available ankle-brachial index measurements. We defined clinical PAD as ankle-brachial index ≤ 0.90 or > 1.40 , and borderline PAD as ankle-brachial index > 0.90 and ≤ 1.00 . We compared the distribution of sociodemographic variables, biomarkers, and comorbidities across PAD classifications. To identify associated factors, we calculated unadjusted and age-sex-adjusted prevalence ratios (PRs) with log-binomial models. Overall, 6.6% (95% CI, 5.6–7.7) of the sample met the diagnostic criteria for clinical PAD, while 44.7% (95% CI, 42.4–47.0) met the diagnostic criteria for borderline PAD. Age (PR: 1.9 [95% CI, 1.2–3.1] for ages 50–59 years compared with 40–49 years; PR: 2.5 [95% CI, 1.5–4.0] for ages 60–69 years compared with 40–49 years); diagnosed hypertension (PR: 1.53 [95% CI, 1.08–2.17]); and C-reactive protein (PR: 1.08 [95% CI, 1.03–1.12]) were associated with increased prevalence of clinical PAD. All other examined factors were not significantly associated with clinical PAD.

CONCLUSIONS: We found high PAD prevalence for younger age groups compared with previous research and a lack of statistical evidence for the influence of traditional risk factors for this rural, low-income population. Future research should focus on identifying the underlying risk factors for PAD in this setting. South African policymakers and clinicians should consider expanded screening for early PAD detection in rural areas.

Key Words: peripheral artery disease ■ prevalence ■ risk factors ■ South Africa

People in low- and middle-income countries (LMICs) are living longer, and the incidence of important chronic diseases associated with aging is rapidly increasing.^{1,2} People in LMICs are also more likely to live in rural settings than people in high income countries and this rurality causes additional resource

challenges.³ Within this context of ongoing demographic and disease burden transitions across LMICs, it is critical to better manage preventable conditions to reduce healthcare costs, reduce the burden on resource-constrained health systems, and promote healthy longevity.

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RESEARCH PERSPECTIVE

What is New?

- Despite all participants being age <70 years, nearly half of the sample met the diagnostic criteria for borderline peripheral artery disease.
- Most traditional risk factors were not statistically different across the strata of peripheral artery disease, with age and C-reactive protein being the primary factors significantly associated with the presence of clinical peripheral artery disease.

What Question Should Be Addressed Next?

- Future research should focus on identifying the unknown, underlying risk factors that influence the high rates of peripheral artery disease observed in this rural South African population.

Nonstandard Abbreviations and Acronyms

HAALSI	Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community
INDEPTH	The International Network for the Demographic Evaluation of Populations and Their Health

One chronic disease important in this context is peripheral artery disease (PAD), an atherosclerotic disorder that predominantly affects the arterial vasculature of the lower extremities and contributes to reduced quality of life as well as increased risk of major adverse cardiovascular events and premature death.^{4–6} From 2015 estimates for sub-Saharan Africa, PAD contributed 20 disability-adjusted life-years (DALYs) per 100 000 with South Africa having the highest burden for the region and a higher burden than observed in high-income countries.⁷ In fact, 73% of the global burden of PAD is concentrated in LMICs with particularly high prevalence estimates in sub-Saharan Africa where traditional risk factors are known to be poorly controlled.^{7,8} Drawing on the evidence base established in high-income settings, smoking is one of the strongest risk factors for PAD development.⁵ Prior history of diabetes and hypertension are also independently predictive of PAD risk.^{5,6}

Interestingly, there is also evidence that the risk factor profile for PAD may differ in sub-Saharan African populations compared with populations in high-income countries, making PAD more difficult to predict and,

thus, more difficult to identify and manage. For example, in sub-Saharan Africa, PAD prevalence is significantly higher among women compared with men.^{9–12} In contrast, few sex differences have been observed for PAD prevalence in high-income countries.⁷ Despite this preliminary evidence, the existing literature for PAD in sub-Saharan Africa comes from clinical samples and disease modeling efforts, representing significant limitations in the literature.^{7,9–14} Thus, further research in sub-Saharan African countries is needed to better understand the burden and risk profile for PAD.

For PAD, rural South Africa is an understudied location with an important distribution of sociodemographic and comorbid risk factors such as high HIV prevalence, low socioeconomic status, and high burden of multi-morbid chronic diseases.^{15–17} We used data from the HAALSI (Health and Aging in Africa: A Longitudinal Study of the International Network for the Demographic Evaluation of Populations and their Health [INDEPTH] Community) cohort, a population-representative cohort of rural and low-income South Africans aged 40 years and older, to quantify the burden and risk factor profile of PAD. This analysis contributes to the literature as a contemporary PAD burden study specific to rural South Africans.

METHODS

Data Set and Source Population

This analysis used data from the HAALSI cohort study of older adults in rural South Africa. The HAALSI cohort was recruited in Agincourt, South Africa, and includes 3 waves of data collection (years 2014/2015, 2017/2018, and 2019/2021). The HAALSI cohort is nested within the Agincourt Health and Demographic Surveillance System, which maintains a research platform that fully enumerates the population living across 31 villages (population 118 000+) in the rural Mpumalanga Province.¹⁸ In 2014, potential participants were randomly selected for invitation to join the cohort from a sampling frame of all individuals aged ≥40 years in the study area.¹⁶ The complete HAALSI cohort consisted of 5,059 men and women at baseline.¹⁶ This sample is not nationally representative but is considered to be representative of the rural South African community from which it was sampled.¹⁶ Following enrollment and consent, household respondents participated in baseline in-person interviews, physical measurements, and voluntary point-of-care biomarker testing.¹⁶ In-person interviews collected data on sociodemographic characteristics, household members, household consumption and spending, employment, social conditions, cognition, self-reported health status, health behaviors, and healthcare utilization. Long-term outcomes including major adverse cardiovascular

events and death were collected for participants in Waves 2 and 3, though not explored in this analysis. A random sub-sample of 1,937 participants below the age of 70 years participated in supplemental data collection that included additional cognitive, physical, and laboratory measurements.¹⁹ Anonymized data and materials for the HAALSI cohort Wave 1 sample and Wave 1 laboratory sample are publicly available through the Harvard Dataverse and can be accessed at <https://doi.org/10.7910/DVN/F5YHML> and <https://doi.org/10.7910/DVN/TW84UI>.

The Agincourt research site served by the Agincourt Health and Demographic Surveillance System is a former homeland area where Black Africans were forcibly moved under the apartheid policy.¹⁸ As such, the HAALSI population composition is almost entirely of Black Africans. Former Mozambican refugees who migrated during the Mozambican Civil War also contribute to the population (~30%).¹⁶ The Agincourt area has high rates of unemployment, high fertility rates, high HIV prevalence, and low access to key infrastructure compared with the general population.^{16,18} The HAALSI study has ethical approvals from the Mpumalanga Provincial Research and Ethics Committee, the University of the Witwatersrand Human Research Ethics Committee (ref. M141159), and the Harvard T.H. Chan School of Public Health Office of Human Research Administration (ref. C13-1608-02).¹⁶ All participants provided informed consent to participate in the HAALSI cohort. Ethical approvals were also sought from the Indiana University Institutional Review Board where it was deemed not human subjects research as the analysis was conducted on deidentified data sets (ref. 18808).

Study Sample

We used HAALSI baseline data collected between November 2014 and November 2015 as well as HAALSI's baseline laboratory data set to perform this cross-sectional analysis. To be included in this study, participants must have participated in the baseline household survey and selected for and participated in the supplemental laboratory testing. Only participants younger than age 70 years were eligible for the supplemental laboratory testing. The laboratory sample was derived from a random sample of the baseline HAALSI cohort. We identified 1883 participants aged 40 to 69 years for inclusion based on having available ankle-brachial index (ABI) data. Fifty-four individuals were excluded from our analysis because they did not have sufficient data to calculate an ABI.

Peripheral Artery Disease

PAD was the primary outcome of interest for this study. No information on treatment or previous diagnosis for

PAD was collected during HAALSI. We identified cases of clinical and borderline PAD among participants with available ABI measurements. ABI is the most common, noninvasive diagnostic measure for PAD and represents the ratio of systolic blood pressure in an individual's ankle to their brachial artery.^{5,6} During HAALSI's supplemental laboratory testing, 2 systolic blood pressure measurements were recorded in millimeters of mercury (mmHg) for each of the following arteries: left dorsalis pedis, right dorsalis pedis, left posterior tibial, right posterior tibial, left brachial, and right brachial. An average of the 2 measurements was calculated for each artery. Then to calculate the ABI, 3 steps were sequentially completed for both the left and right leg: (1) We identified the higher systolic blood pressure of the 2 leg measurements (dorsalis pedis or posterior tibial); (2) We divided the leg measurement by the higher of 2 brachial systolic blood pressures (right or left); and (3) We recorded the lower ABI value of the 2 legs (right or left) to 2 decimal places.²⁰

In line with consensus guidelines from the American Heart Association, clinical PAD was defined as an ABI of ≤ 0.90 or > 1.40 while borderline PAD was defined as an ABI > 0.90 and ≤ 1.00 .⁴⁻⁶ Participants were considered to have no indications of PAD if their ABI was > 1.00 and ≤ 1.40 . Binary indicator variables were coded for both clinical PAD and borderline PAD based on the above definitions. Cases were coded as 1 for each variable and non-cases were coded as 0.

Comorbidities and Sociodemographic Characteristics

We examined a set of sociodemographic characteristics, biomarker measures, and comorbidities to characterize the population and examine traditional risk factors that have been established within the existing literature.^{4,5,21} Sociodemographic characteristics used in our analyses included sex (men versus women), age (in years), education level (none, primary or some secondary, versus secondary or higher), place of birth (within South Africa versus outside South Africa), prior occupational smoke exposure (yes versus no), smoking status (current smoker, ever-smoker, versus non-smoker), and current alcohol drinking status (yes versus no). All sociodemographic variables were collected via self-report during the HAALSI baseline in-person survey.

Biomarker measures used in our analyses included high-density lipoprotein cholesterol (in mmol/L), low-density lipoprotein cholesterol (in mmol/L), total cholesterol (in mmol/L), triglycerides (in mmol/L), blood glucose (in mmol/L), diastolic blood pressure (in mmHg), systolic blood pressure (in mmHg), hemoglobin (in grams per deciliter [g/dL]), and CRP (C-reactive protein) (in mg/L). All biomarker measures were taken

during the baseline in-person interview via point-of-care blood testing, dried blood spot testing, and blood pressure testing, using previously described methodologies.²²

We assessed the following comorbidities among participants: HIV status, diabetes, dyslipidemia, hypertension, obesity, prior major adverse cardiovascular event, and kidney disease. Binary variables for HIV status, prior major adverse cardiovascular events, and kidney disease were identified via participant self-reports. Prior major adverse cardiovascular event was defined as any prior myocardial infarction, stroke, heart failure, or angina. Diabetes was defined as a participant who self-reported a diabetes diagnosis, was fasting with a glucose measurement of ≥ 7.00 mmol/L, or was not fasting with a glucose measurement of ≥ 11.10 mmol/L.²³ Dyslipidemia was defined as a participant with a self-reported diagnosis of high cholesterol and/or total cholesterol of ≥ 6.21 mmol/L, high-density lipoprotein cholesterol of ≤ 1.19 mmol/L, low-density lipoprotein cholesterol of > 4.1 mmol/L, or triglycerides > 2.25 mmol/L. Hypertension was defined in participants with self-reported current use of anti-hypertensive medication and/or systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg.²⁴ We also defined a binary variable indicating the presence of any of the following cardiometabolic conditions: diabetes, dyslipidemia, hypertension, or obesity.

Statistical Analysis

We compared the distribution of sociodemographic variables, biomarkers, and comorbidities across the 3 PAD classifications: no PAD, clinical PAD, and borderline PAD. We then estimated the crude prevalence of clinical and borderline PAD across the total population and stratified across levels of each primary risk factor. To identify factors associated with clinical and borderline PAD in this setting, we calculated unadjusted and age-sex-adjusted prevalence ratios (PRs) for each identified PAD risk factor. PRs were estimated with log-binomial models and reported with 95% CIs. We constructed separate models for clinical and borderline PAD. For the clinical PAD models, the reference group was all individuals with no PAD or borderline PAD. For the borderline PAD models, the reference group was all individuals with no PAD. Clinical PAD cases were excluded from the borderline PAD analysis. All analyses were performed as a complete case analysis.

Additionally, we conducted a sensitivity analysis to further explore the relationship between hypertension and PAD given the high prevalence of hypertension among the HAALSI population and because it has been identified as a primary risk factor for cardiovascular diseases in sub-Saharan Africa. For this analysis, we estimated age-sex-adjusted prevalence ratios via log-binomial models and reported with 95% CIs for

the following exposure comparisons: no high blood pressure versus high blood pressure (through testing only, not including self-reports), no hypertension diagnosis versus self-reported hypertension diagnosis, not taking hypertension medication versus taking hypertension medication (among those with a hypertension diagnosis), and across 4 groups defined using systolic blood pressure measurements: < 140 , 140 to 159, 160 to 179, and > 179 mmHg, with the < 140 mmHg group used as the reference. All statistical analyses were conducted using R version 4.1.1.²⁵

RESULTS

Study Population

Our analytic cohort consisted of 1883 HAALSI participants aged 40 to 69 years with complete ABI data. Over half (58.8%) of participants in this sample were women, and approximately one-third (32.4%) had no formal education. Eighty-four percent of participants met the diagnostic criteria for at least 1 cardiometabolic disease, and 5% reported a previous major adverse cardiovascular event (see [Table 1](#)). Approximately 60% of the sample met the criteria for hypertension, 10% for diabetes, and 33% for obesity (see [Table S1](#)). The prevalence of hypertension and obesity was significantly greater in women compared to men.

PAD Status

Overall, 6.6% (95% CI, 5.6%–7.7%) of the sample met the diagnostic criteria for clinical PAD while 44.7% (95% CI, 42.4%–47.0%) met the diagnostic criteria for borderline PAD (see [Table 2](#)). Clinical PAD was most prevalent among participants who were aged 60 to 69 years (9.3% [95% CI, 6.9%–12.1%]), were current alcohol drinkers (8.2% [95% CI, 5.6%–11.4%]), had a high waist-to-hip ratio (9.8% [95% CI, 5.5%–15.9%]), had a previous major adverse cardiovascular event (9.4% [95% CI, 4.4%–17.0%]), and had diabetes (9.7% [95% CI, 5.7%–15.0%]). Borderline PAD was most prevalent among participants who were women (48.7% [95% CI, 45.7%–51.7%]), were aged 40 to 49 years (48.7% [95% CI, 44.6%–52.8%]), and were current smokers (53.6% [95% CI, 46.3%–60.8%]).

Prevalence Ratios by Clinical PAD

Age and CRP were the only risk factors significantly associated with a higher prevalence of clinical PAD (see [Figure 1](#)). After adjusting for sex, the 50-to-59-year age group was associated with nearly 2 times the prevalence of clinical PAD compared with the 40-to-49-year age group (PR: 1.9 [95% CI, 1.2–3.1]), while the 60-to-69-year age group was associated with 2.5 times the prevalence of clinical PAD compared with the 40-to-49-year age group (PR: 2.5 [95% CI, 1.5–4.0]).

Table 1. Sociodemographic Characteristics and Risk Factors Across PAD Diagnostic Categories

	No PAD (n=916)	Borderline PAD (n=842)	Clinical PAD (n=125)
Mean age, y	53.97 (8.3)	53.05 (8.0)	56.62 (7.8)
Men, %	45.6 (1.6)	36.0 (1.6)	44.0 (4.4)
South African nationality, %	71.3 (1.5)	71.1 (1.6)	75.2 (3.9)
Current smoker, %	8.3 (0.9)	12.3 (1.1)	10.4 (2.7)
Current drinker, %	19.1 (1.3)	20.5 (1.4)	24.8 (3.9)
Any CVD, %	5.7 (0.8)	4.2 (0.7)	7.2 (2.3)
Any cardiometabolic disease, %	84.0 (1.2)	83.2 (1.3)	85.1 (3.2)
Mean waist-to-hip ratio	0.90 (0.1)	0.90 (0.1)	0.92 (0.1)
Mean BMI, kg/m ²	27.78 (6.6)	27.91 (7.3)	27.88 (6.5)
Mean waist circumference, cm	93.64 (15.6)	92.39 (15.4)	95.00 (16.2)
Mean HDL, mmol/L	1.55 (0.5)	1.58 (0.5)	1.59 (0.6)
Mean LDL, mmol/L	2.09 (1.0)	2.02 (1.0)	2.15 (1.1)
Mean total cholesterol, mmol/L	4.17 (1.2)	4.16 (1.2)	4.35 (1.3)
Mean triglycerides, mmol/L	1.75 (0.9)	1.73 (0.9)	1.84 (1.1)
Mean glucose, mmol/L	6.56 (2.9)	6.38 (3.1)	7.11 (4.2)
Mean diastolic BP, mmHg	83.62 (12.1)	82.98 (11.8)	85.08 (14.1)
Mean systolic BP, mmHg	136.10 (21.8)	133.36 (20.6)	142.45 (24.2)
Mean hemoglobin, g/dL	12.59 (1.9)	12.63 (2.0)	12.51 (1.9)
Mean CRP, mg/L	2.96 (2.9)	2.98 (3.1)	3.92 (3.6)

Mean (SD) presented for continuous variables; % (SE) presented for dichotomous variables. BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and PAD, peripheral artery disease.

After adjusting for age and sex, the prevalence of clinical PAD increased by 8% for every 1 mg/L increase in CRP (PR: 1.08 [95% CI, 1.03–1.12]).

Prevalence Ratios by Borderline PAD

Sex, age, current smoking status, and current drinking status were significantly associated with borderline PAD prevalence (see [Figure 2](#)). Men had a 20% lower prevalence of borderline PAD compared with women, after adjusting for age (PR: 0.8 [95% CI, 0.7–0.9]). The 60-to-69-year age group was also associated with an ≈20% decrease in the prevalence of borderline PAD compared with the 40-to-49-year age group (PR: 0.8 [95% CI, 0.7–0.9]). Being a current smoker (PR: 1.6 [95% CI, 1.3–1.9]) and a current alcohol drinker (PR: 1.2 [95% CI, 1.0–1.3]) were each independently associated with a higher prevalence of borderline PAD after adjusting for age and sex.

Hypertension Sensitivity Analysis

High blood pressure identified via blood pressure testing and self-reported current hypertension medication (among diagnosed hypertensives) were not associated with the prevalence of borderline or clinical PAD (see [Table S2](#)). Self-reported hypertension diagnosis compared with no current hypertension diagnosis was associated with 1.5 times the prevalence of clinical PAD (PR: 1.5 [95% CI, 1.1–2.2]). Across the 4-level systolic blood pressure variable, only a systolic measurement

of 160 to 179 mmHg was significantly associated with an increased prevalence of clinical PAD compared with a systolic measurement of <140 mmHg (PR: 1.9 [95% CI, 1.2–3.1]).

DISCUSSION

We conducted an analysis of the HAALSI cohort to provide a contemporary estimate of PAD prevalence for a rural South African population. We estimated that the prevalence of clinical PAD in this representative sample of adults aged 40 to 69 years was 6.6%. Also, despite a mean age of 54 years, nearly half of our sample met the diagnostic criteria for borderline PAD. Most traditional risk factors (eg, smoking, diabetes, and hypercholesterolemia) were similar across strata of PAD. Age and CRP were the only factors significantly associated with clinical PAD while age, sex, current smoking status, and current alcohol drinking status were significantly associated with borderline PAD. Though our definition of hypertension (which included both self-reports and high blood pressure measurements) was not associated with the prevalence of clinical PAD, we did find that a self-reported hypertension diagnosis alone was significantly associated with an increased prevalence of clinical PAD.

Our estimate of clinical PAD prevalence was lower than previous studies from sub-Saharan Africa which range from 14% to 38%.^{9,10,12,26} However, these studies

Table 2. Estimated Prevalence of Clinical and Borderline Peripheral Artery Disease (PAD), Stratified by Demographic and Risk Factors

	Borderline PAD (n=842), % (95% CI)	Clinical PAD (n=125), % (95% CI)
Total (n=967)	44.72 (42.45–46.99)	6.64 (5.56–7.86)
Sex		
Male (n=358)	39.05 (35.60–42.58)	7.09 (5.38–9.13)
Female (n=609)	48.69 (45.71–51.68)	6.32 (4.96–7.92)
Age group		
40–49y (n=310)	48.73 (44.63–52.84)	3.72 (2.35–5.58)
50–59y (n=421)	45.79 (42.28–49.32)	7.17 (5.48–9.19)
60–69y (n=236)	38.23 (33.94–42.66)	9.26 (6.86–12.15)
Education level		
None (n=305)	42.95 (38.98–46.99)	7.05 (5.15–9.38)
Primary or some secondary (n=556)	46.53 (43.48–49.60)	6.37 (4.97–8.03)
Secondary or higher (n=103)	40.18 (33.63–47.00)	6.85 (3.88–11.05)
Born in South Africa		
No (n=274)	45.25 (40.98–49.57)	5.77 (3.96–8.09)
Yes (n=693)	44.50 (41.82–47.20)	6.98 (5.68–8.48)
Occupational smoke exposure		
No (n=794)	45.03 (42.52–47.55)	6.56 (5.38–7.92)
Yes (n=172)	43.15 (37.84–48.58)	7.00 (4.53–10.23)
Smoking status		
Nonsmoker (n=644)	44.52 (41.97–47.09)	6.46 (5.26–7.83)
Ever-smoker (n=207)	37.13 (30.45–44.19)	7.92 (4.60–12.54)
Current smoker (n=116)	53.65 (46.32–60.85)	6.77 (3.65–11.30)
Current alcohol drinker		
No (n=763)	44.48 (41.95–47.03)	6.25 (5.08–7.59)
Yes (n=204)	45.65 (40.55–50.81)	8.18 (5.63–11.41)
Waist-to-hip ratio		
Low (n=224)	45.33 (40.60–50.12)	5.69 (3.72–8.29)
Moderate (n=641)	45.45 (42.65–48.27)	6.20 (4.93–7.69)
High (n=71)	39.86 (31.77–48.38)	9.79 (5.46–15.88)
Obese		
No (n=629)	44.20 (41.42–47.02)	6.44 (5.14–7.95)
Yes (n=326)	46.04 (42.06–50.06)	6.62 (4.79–8.88)
HIV status		
HIV-negative (n=623)	43.66 (40.86–46.50)	7.28 (5.88–8.88)
HIV-positive (n=281)	47.30 (43.01–51.62)	5.03 (3.34–7.23)
Previous major adverse cardiovascular event		
No (n=923)	45.16 (42.83–47.50)	6.49 (5.39–7.73)
Yes (n=44)	28.57 (17.30–42.21)	9.38 (4.38–17.05)
Diabetes		
No (n=832)	45.36 (42.91–47.84)	6.41 (5.26–7.72)
Yes (n=86)	39.20 (31.95–46.83)	9.66 (5.73–15.01)
Dyslipidemia		
No (n=475)	45.72 (42.42–49.05)	7.12 (5.53–9.00)
Yes (n=377)	43.26 (39.68–46.89)	7.08 (5.35–9.15)

(Continued)

Table 2. Continued

	Borderline PAD (n=842), % (95% CI)	Clinical PAD (n=125), % (95% CI)
Hypertension		
No (n=400)	47.31 (43.72–50.93)	5.11 (3.66–6.92)
Yes (n=560)	42.95 (40.01–45.93)	7.69 (6.18–9.42)

focused primarily on populations older than 60 years while our population was between 40 and 69 years. In contrast, our prevalence measures were higher than prior estimates from LMIC settings performed in similar age groups. Studies from the Philippines, Malawi, and China estimated a prevalence of PAD ranging from 2% to 5% for comparable age groups.^{27–30} Similarly, a previous global analysis concluded that LMICs have higher PAD prevalence at younger ages compared with high-income countries.⁸ We estimated the prevalence of clinical PAD in HAALSI participants aged 40 to 49 years as well as aged 50 to 59 years to be over 2 times higher than estimates from the United States.³¹ This high prevalence implies the need for early intervention to slow and reduce PAD risk for South African adults.

We found that nearly half of HAALSI participants who were assessed for PAD had a borderline ABI measurement between 0.91 and 1.00. In contrast, borderline PAD prevalence has been measured at between 9% and 17% across a variety of settings.^{29,32–35} Additionally, our prevalence estimate of clinical PAD is significantly lower than the one previous study conducted in rural South Africa in 2007 which estimated a clinical PAD prevalence of 29.3%.³⁶ However, differences in the age distribution of the samples, with our study population being younger, as well as the source of the samples (clinical sample versus population-based sample) may account for the differences. Borderline ABI is a sign of premature atherosclerotic disease and is associated with a higher risk of coronary heart disease, adverse vascular events in the leg, and progression to clinical PAD compared with normal ABI.^{35,37} Therefore, without proper identification and management, a significant percent of this rural South African population may be at high risk for future disease progression and major adverse cardiovascular events. This risk is even more pronounced given that >80% of the population also suffers from at least 1 cardiometabolic disease. Future research should assess the benefits of early PAD detection for high-risk groups in LMIC settings as a strategy to reduce downstream adverse cardiovascular events and premature death.

PAD risk factors may differ in sub-Saharan Africa compared with high-income countries. For example, PAD is significantly higher among women and associated with both underweight and obesity.^{9–11,38} This is different from high-income settings, like the United

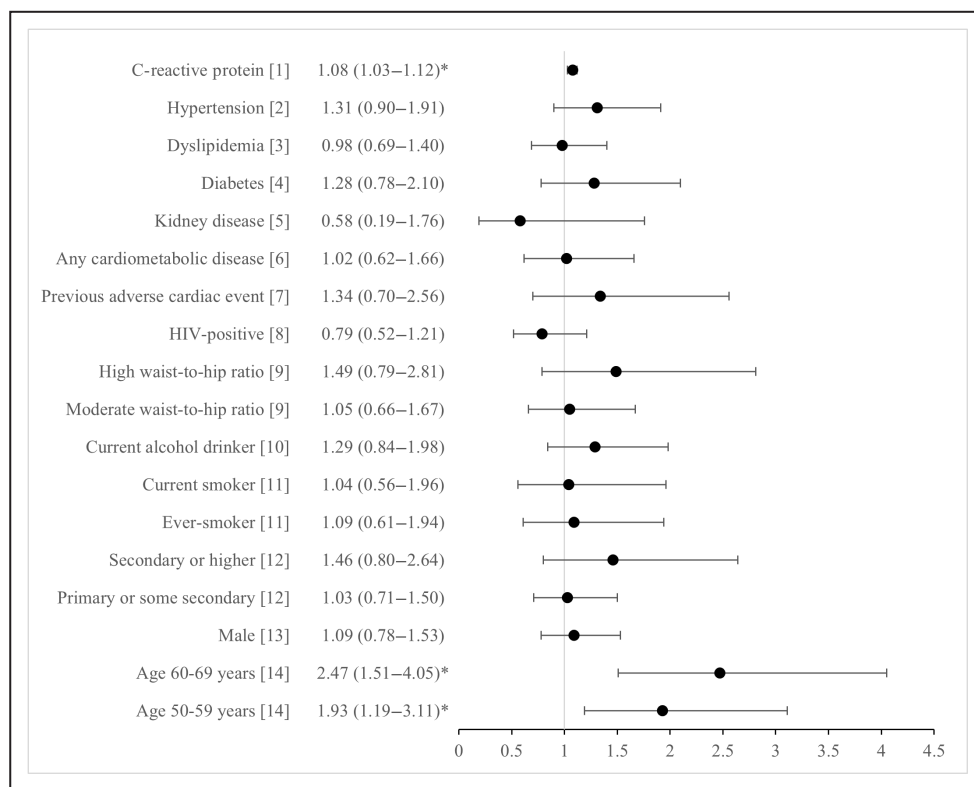


Figure 1. Age- and sex-adjusted prevalence ratios of clinical peripheral artery disease.

*Statistically significant at $\alpha=0.05$; [1] $n=1768$, mg/dL; [2] $n=1869$, reference: no hypertension; [3] $n=1648$, reference: no dyslipidemia; [4] $n=1783$, reference: no diabetes; [5] $n=1882$, reference: no kidney disease; [6] $n=1794$, reference: no cardiometabolic disease; [7] $n=1883$, reference: no previous adverse cardiac event; [8] $n=1760$, reference: HIV-negative; [9] $n=1823$, reference: low waist-to-hip ratio; [10] $n=1883$, reference: not a current alcohol drinker; [11] $n=1881$, reference: never smokers; [12] $n=1880$, reference: no education; [13] $n=1883$, reference: women; [14] $n=1883$, reference: age 40 to 49 years.

States, where there are little sex differences in PAD prevalence.⁸ The sex differences are particularly interesting considering that traditional risk factors, such as smoking, tend to be lower among women in LMIC settings.⁸ High rates of obesity and hypertension were found among women in the HAALSI population which may contribute to the development of PAD. However, we found that most traditional risk factors (diabetes, dyslipidemia, smoking, alcohol drinking, and obesity) were not significantly associated with a higher likelihood of having clinical PAD. In fact, only CRP and age were positively and significantly associated with PAD in our study. However, the direction of effect trended consistently towards greater prevalence of PAD for the traditional high-risk groups. It is possible that our models were not powered appropriately to detect a significant difference for these traditional risk factors. The association between CRP and PAD is supported by previous studies from high-income countries.^{8,39} We also found that being a current smoker or current alcohol drinker was associated with borderline PAD status, findings in line with prior literature.^{5,8} Together, this suggests that unknown underlying risk factors are

likely influencing the high rates of PAD observed in the HAALSI population.

Alternative potential risk factors for PAD in this population include endemic infectious diseases, chronic stress, and air pollution. Preliminary ecological evidence shows an association between PAD prevalence and country-level burdens of endemic infectious diseases like HIV, tuberculosis, and malaria.⁴⁰ Historically, rural South Africa has had a high infectious disease burden, including HIV. Approximately 23% of the HAALSI population is HIV-positive with South Africa having one of the highest HIV burdens globally.¹⁶ Additionally, chronic stress may be a critical factor in the formation of atherosclerosis via the impacts of chronic inflammation.⁴¹ The historical context of apartheid and the low-income, high unemployment environment of the Agincourt sub-district has likely led to high levels of lifetime stress for HAALSI participants. This high-stress environment may be contributing to the early development of PAD indicated by the prevalence of borderline ABIs. Finally, associations have been observed between long-term exposure to air pollutants, including carbon monoxide and particulate matter, and PAD.⁴² While outdoor

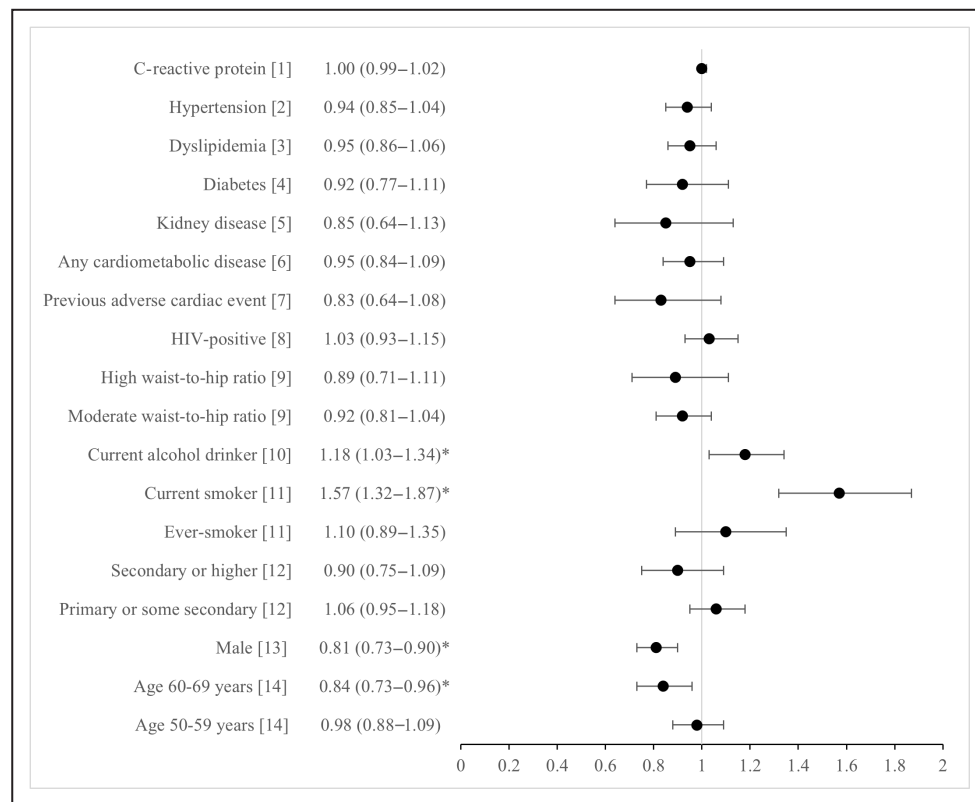


Figure 2. Age- and sex-adjusted prevalence ratios of borderline peripheral artery disease.

*Statistically significant at $\alpha=0.05$; [1] $n=1650$, mg/dL; [2] $n=1745$, reference: no hypertension; [3] $n=1531$, reference: no dyslipidemia; [4] $n=1663$, reference: no diabetes; [5] $n=1757$, reference: no kidney disease; [6] $n=1673$, reference: no cardiometabolic disease; [7] $n=1758$, reference: no previous adverse cardiac event; [8] $n=1644$, reference: HIV-negative; [9] $n=1707$, reference: low waist-to-hip ratio; [10] $n=1758$, reference: not a current alcohol drinker; [11] $n=1756$, reference: never smokers; [12] $n=1755$, reference: no education; [13] $n=1758$, reference: women; [14] $n=1758$, reference: age 40 to 49 years.

air pollution is not substantial in the Agincourt area, HAALSI participants may be exposed to high levels of indoor air pollutants from indoor biomass cooking.⁴³ While the linkage between indoor air pollution and PAD is limited, prior research in Malawi found an association between indoor fire exposure and lower extremity disease while other work in sub-Saharan Africa has found an increased risk of cardiovascular disease associated with indoor biomass cooking.^{27,44–46} These risk factors warrant future exploration in the HAALSI cohort.

As the only factor other than age associated with clinical PAD in this study, CRP demonstrates the possible importance of life stressors and inflammation in the development of PAD and other atherosclerotic conditions. Chronic stress has been identified as a risk factor for atherosclerosis, particularly through its link to chronic inflammation.⁴⁷ CRP is one measure of inflammation associated with cardiovascular disease that is likely influenced by both acute infections and stress exposure over the life course.^{48–50} This setting of

rural South Africa is a population with both high exposure to chronic stressors and high infectious disease burdens. A high proportion of the HAALSI population has experienced ≥ 1 traumatic events throughout their life including severe financial hardship, life-threatening illnesses, death of a close family member/friend from violence, and physical abuse by parents.⁵¹ The underlying history of apartheid may also contribute to this, creating a unique environment characterized by high stress across the life course.

The primary limitation of this study is its cross-sectional nature. Because of this design, we cannot confirm the temporal link between the examined risk factors and the development of PAD. However, future work can exploit the additional waves of data collection from the HAALSI cohort to create a more nuanced picture of PAD development and progression for this population. Additionally, only a subsample of HAALSI participants were included in this analysis and no one above the age of 69 years was included. Therefore,

this analysis is not representative of the total population affected by PAD and primarily describes cases with early onset. PAD is a condition that increases in prevalence with age, thus, our analysis is likely missing a large proportion of prevalent cases within individuals aged >69 years. However, a comparison of key sociodemographic characteristics in the full HAALSI sample of individuals aged <70 years to the subset used in this analysis showed few differences. Because of the smaller sample size compared with the total HAALSI population, our study may not be powered appropriately to detect significant differences across all traditional risk factors. Despite these limitations, our analysis is strengthened by the use of the ABI as an objective diagnostic measure for PAD.

CONCLUSIONS

Our study is among the first recent attempts to quantify PAD burden and profile potential risk factors in rural South Africa using data from a representative, population-based survey. Most notably, we found that nearly half of HAALSI participants met the diagnostic criteria for borderline PAD. As the population of this study ranged from 40 to 69 years, this represents a large proportion with borderline disease at a younger age than has been previously documented in the literature. We also found that age and CRP were the only factors significantly associated with clinical PAD. No other traditional risk factors were found to significantly predict clinical PAD in this population. Future research should focus on identifying the unknown, underlying risk factors that influence the high rates of PAD observed in this population. South African policymakers and clinicians should consider expanded screening for early PAD detection in rural areas.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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