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Association between self-rated health, cardiovascular risk factors and echocardiography: A study from the Amazon Basin, Brazil

Short title: Self-rated health and cardiac disease in the Amazon

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Abstract

Objective: Self-rated health is associated with cardiovascular mortality. We assessed the relationship between self-rated health, cardiovascular risk factors, and subclinical cardiac disease in the Amazon Basin.

Setting: Cross-sectional study where self-rated health was obtained according to a visual analogue scale, ranging from 0 (poor) to 100 (excellent). We performed questionnaires, physical examination, and echocardiography. Logistic and linear regression models were applied to assess self-rated health, cardiac risk factors and cardiac disease by echocardiography. Multivariable models were mutually adjusted for other cardiovascular risk factors, clinical and socioeconomic data, and known cardiac disease.

Results: A total of 574 participants (mean age 41 years, 61% female) provided information on self-rated health (mean 75 ± 21 [interquartile range 60 to 90] points). Self-rated health (per 10-point increase) was negatively associated with hypertension (OR 0.87 [95%CI 0.78-0.97], P=0.01), hypercholesterolemia (OR 0.89 [95%CI 0.80-0.99], P=0.04) and positively with healthy diet (OR 1.13 [95%CI 1.04-1.24], P=0.004). Sex modified these associations (P-interaction<0.05) such that higher self-rated health was associated with healthy diet and physical activity in men, and lower odds of hypertension and hypercholesterolemia in women. No relationship was found with left ventricular ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P=0.22), left ventricular hypertrophy (OR 0.89 [95%CI 0.78 to 1.02], P=0.09), or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47).

Conclusion: Self-rated health was positively associated with health parameters in the Amazon Basin, but not with subclinical cardiac disease by echocardiography. Assessment

of self-rated health could be useful for screening or as a target in healthcare policies for lifestyle interventions.

Words: 254

Keywords: self-rated health; cardiovascular risk factors; echocardiography, low and middle-income countries

Article summary

Strengths and limitations

- Self-rated health was positively associated with a healthy lifestyle, and this relationship was modified by sex.
- Importantly, self-rated health was not associated with cardiac disease by echocardiography.
- Healthcare policies could potentially utilize self-rated health for cardiovascular risk screening or as a target to improve health behavior.

Introduction

Cardiovascular disease is the leading cause of mortality worldwide and accounts for more than 31% of all deaths and 8% of public hospitalizations in Brazil [1,2]. Since the 1960s, Brazil has experienced a transition in health behavior and cardiovascular risk factors, where tobacco consumption has declined and obesity has increased [3]. Approximately 35% of Brazilian adults suffer from hypertension [4], the prevalence of diabetes mellitus is rising [5], and a high proportion of adults do not practice recommended levels of physical activity [1]. Differences in perception of risk factors and variability in access to healthcare unequivocally affect health behavior and the lifetime risk of cardiovascular disease. In this regard, self-rated health is widely used as a health indicator in various populations [6], is strongly associated with cardiovascular morbidity [7,8], and provides prognostic information on mortality [9]. Self-rated health and cardiovascular risk factors are also both influenced by sex [10,11]. Throughout the last decades, assessment of self-rated health has become increasingly important and is often used for healthcare surveillance and in policy making.

The aim of this study was to assess whether self-rated health is related to cardiovascular risk factors and disease in the general population from the Amazon Basin of Brazil. We hypothesized that higher self-rated health is associated with less cardiovascular risk factors and disease, and that these relationships are modified by sex [12].

Methods

Study site

The study was conducted in the municipality of Cruzeiro do Sul, Acre (Northern Brazil; Amazon Basin). The prevalence for cardiovascular disease in Acre (5,815 per 100,000 inhabitants) is below the average rate for Brazil (6,025 per 100,000 inhabitants) and [2] the region is considered to be one of the poorest in Brazil and has one of the lowest population densities [13].

Patient and Public Involvement

Patients or the public were not involved in the study design, recruitment to and conduct of the study nor reporting of results. All patients were informed of the results from their own examinations conducted in the study.

Data will be made available upon reasonable request to the corresponding author.

Sampling

This cross-sectional study was conducted as a part of the Malaria Heart Study (clinicaltrials.gov: NCT04445103). Participants from the general population were enrolled from June 2020 through December 2020. Through randomization, we selected 10 local healthcare clinics from Cruzeiro do Sul, equally distributed between rural and urban areas. Local healthcare agents provided lists of persons associated with each clinic from which a random sample was invited to participate in the study. We included persons ≥18 years old

who completed the examination program and responded to all questionnaires. Exclusion criteria were ongoing pregnancy, ongoing infection as assessed by examination of a medical doctor, and presence of *Plasmodium* in peripheral blood smears. A total of 504 participants were included from healthcare clinics. A second group of 70 participants from the general population who had recently completed anti-malarial treatment, and for whom the above-mentioned inclusion and exclusion criteria also applied, were included as well.

Data collection

Two different questionnaires were administered by trained interviewers. The first was the EQ-5D-5L questionnaire which is validated in Brazilian Portuguese (study registration no.: 28276) [14]. For the purpose of this study, we used data from the EQ visual analogue scale (EQ-VAS) which provides a single estimate of self-rated health ranging from 0 to 100 points on a continuous scale. Zero represents the worst possible self-rated health and 100 represents ideal health. The second questionnaire was used to gather information about socioeconomic status, race, cardiovascular risk factors, known cardiac disease (prior myocardial infarction and heart failure), and current medications. Race was self-reported, and two persons did not answer this question. Afterwards, participants underwent a physical examination to measure height, weight, and blood pressure. Fingerstick point-of-care blood draws were used to measure glucose levels and to obtain thick and thin blood slides. Giemsa stained thick and thin blood slides were analyzed by two independent microscopists to detect *Plasmodium*.

Cardiovascular risk factors

We assessed seven different cardiovascular risk factors. Hypertension was defined as a physician diagnosis of hypertension or intake of anti-hypertensive medication, hypercholesterolemia as a physician diagnosis of dyslipidemia or intake of lipid lowering medication, and diabetes as a physician diagnosis of diabetes or fasting blood glucose >126mg/dL [15]. Body mass index (BMI) was calculated as: body weight (kilograms)/height^2 (meters), and obesity was defined as BMI ≥30kg/m^2. Participants were classified as smokers if they were current smokers or had previously smoked. A healthy diet was defined as intake of any quantity of vegetables with a main meal ≥3 times/week. Physical activity was defined as participation in any kind of physical activity during leisure time. We did not apply any time limit or threshold.

Biochemistry

Field procedures: During examinations, we collected peripheral venous blood samples in citrate, EDTA, and serum-separator tubes, which were cooled at 2-8^{o}C. Citrate plasma was immediately separated by centrifugation (12 minutes, 3200 rpm) in a mobile laboratory and transferred to Eppendorf tubes.

Laboratory: Serum-separator tubes underwent centrifugation (10 min, 3000rpm) to extract serum which was subsequently stored at -20^{o}C in Eppendorf tubes. Laboratory analyses were performed at Citolab and Centro de Diagnósticos, Cruzeiro do Sul, Acre, Brazil. Using EDTA blood, a complete blood count with a differential was conducted (NX-350, Sysmex, Japan; Citolab), and reticulocytes were counted manually (Citolab) [16]. Citrate plasma was used to analyze coagulation parameters (Coagmaster 2.0, Wama

Diagnóstica, Brazil; Citolab). Serum was used to measure creatinine, bilirubin, and C-reactive protein (Cobas c111, Roche Diagnostics, Switzerland; Citolab and Centro de Diagnósticos). Analyses of C-reactive protein were only available in a subset of participants (n=436).

Echocardiography

A single medical doctor either performed or supervised all echocardiographic examinations (PB). Quality control was conducted on a frequent basis in a central imaging laboratory (Herlev-Gentofte Hospital, Denmark) by an investigator certified in echocardiography by the European Association of Cardiovascular Imaging. Examinations were performed bedside (Vivid-IQ, GE Healthcare, Norway), and images were stored offline for analysis in EchoPAC BT13 (v. 203.82). Analyses were conducted by AW according to contemporary guidelines [17]. Rheumatic heart disease was assessed by PB according to the World Heart Federation criteria [18]. We assessed three categories of subclinical left ventricular (LV) cardiac disease: (i) reduced contractile function defined as LV ejection fraction <45%, (ii) LV hypertrophy defined as LV mass index >115g/m^2 for men and >95g/m^2 for women and (iii) diastolic dysfunction determined according to existing guidelines [19]. Classification of diastolic dysfunction involves assessment of early and late mitral inflow velocity, mitral annular early diastolic velocity, tricuspid regurgitation velocity and the left atrial volume index. Additional details are described in Supplemental Data 'Methods'.

Ethics

The study was approved by the institutional review committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467),

local health care authorities and leaders of health care clinics. The study complies with the 2nd Declaration of Helsinki, and all patients provided written informed consent on oral and written information given in Portuguese. Illiterate participants provided fingerprints instead of signatures. For ethical reasons a medical doctor evaluated all participants on-site, and in case of suspected heart disease participants were referred to a cardiologist.

Data from the study is available upon reasonable request to the senior author. Patients or the public were not involved in the study design or reporting of results.

Statistics

Baseline characteristics for the study population were stratified according to tertiles of self-rated health (cut-offs of 70 and 91 points) and sex. Due to the nature of the distribution, tertiles of self-rated health did not contain equal amounts of participants. P for trend was calculated using linear regression models and the Cuzick nonparametric test for trend [20]. Differences between groups were compared using the chi-square test, Student's *t*-test, and the Wilcoxon rank-sum test, as appropriate. Histograms were conducted to display the distribution of self-rated health. In all statistical tests, self-rated health was treated as a continuous variable. Logistic regression models were conducted to examine the relationship between self-rated health and cardiovascular risk factors and disease. Multivariable models were adjusted for core variables: clinical data (age, sex, race), socioeconomic data (work, family income, living area), known cardiac disease (prior myocardial infarction, heart failure, rheumatic heart disease). In addition, all associations with cardiovascular risk factors were mutually adjusted for all other risk factors. Interactions with sex were also examined. Family income was log-transformed to provide a normal distribution. The relationship between self-rated health and (i) the sum of cardiac

risk factors (hypertension, hypercholesterolemia, diabetes, obesity, smoking) and (ii) echocardiographic parameters were assessed in linear regression models, which were adjusted for the core variables. All analyses were conducted in Stata v.14.2 (StataCorp, Texas, USA) and RStudio v.1.3 (R, Vienna, Austria). Two-sided P-values <0.05 were considered statistically significant.

Results

A total of 574 participants were assessed (mean age 41 ± 15 years, 61% female). Mean self-rated health was 75 ± 21 points (interquartile range 60 to 90 points) (Figure 1A). Four participants (<1%) reported 0 points, and 91 participants (16%) reported 100 points. The prevalences of cardiovascular risk factors were 20% for hypertension, 16% for hypercholesterolemia, 6% for diabetes, 23% for obesity, 38% for current or prior smoking, 52% for unhealthy diet, and 63% for absence of physical activity. Participants with lower self-rated health more frequently had all of the above risk factors and were older compared with participants with high self-rated health (P-trend<0.05; Table 1). No differences were observed in socioeconomic characteristics, biochemistry, or subclinical cardiac disease by echocardiography (reduced LV ejection fraction, hypertrophy, diastolic dysfunction) across tertiles of self-rated health (Table 1).

Cardiovascular risk factors

In unadjusted logistic regression models, better self-rated health was significantly associated with lower odds of all cardiovascular risk factors (P<0.05 for all; Table 2). In adjusted models, self-rated health (per 10-point increase) was associated with lower odds of hypertension (OR 0.87 [95%CI 0.78 to 0.97], P=0.01], hypercholesterolemia (OR 0.89 [95%CI 0.80 to 0.99], P=0.04) and higher odds of healthy diet (OR 1.13 [95%CI 1.04 to 1.24], P=0.004). In multivariable models, better self-rated health was also associated with the sum of cardiovascular risk factors (beta = -0.07 per 10-point increase [95%CI -0.10 to -0.03], P<0.001).

Subclinical cardiac disease by echocardiography

No significant associations were found between self-rated health (per 10-point increase) and subclinical cardiac disease by echocardiography: LV ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P= 0.22), LV hypertrophy (OR 0.87 [95%CI 0.72 to 1.07], P=0.19) or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47) (Table 2). No individual echocardiographic parameters were significantly associated with self-rated health in multivariable models (P>0.05 for all; Table 3).

Interactions with sex

Self-rated health was higher in men than in women (77 vs 73 points) but the difference was not statistically significant (P=0.09) (Figure 1B-C). In general, women had higher body mass index, lower income, less frequently smoked, and were more physically active compared with men (P<0.05 for all; Supplemental Table 1). Sex modified the associations with hypertension, smoking, healthy diet, and physical activity, but not cardiac disease by echocardiography (Table 2). Unadjusted associations with cardiovascular risk factors, stratified by sex, are presented in Figure 2. For men, higher self-rated health (per 10-point increase) yielded greater odds of a healthy diet (adjusted OR 1.33 [95%CI 1.12 to 1.59], P=0.002) and physical activity (adjusted OR 1.24 [95%CI 1.03 to 1.50], P=0.02). For women, higher self-rated health (per 10-point increase) was associated with lower odds of hypertension (adjusted OR 0.85 [95%CI 0.74 to 0.97], P=0.016), and hypercholesterolemia (adjusted OR 0.87 [95%CI 0.76 to 0.99], P=0.046).

Discussion

This study has two principal findings. First, in a sample of the general population from the Amazon Basin, we found that self-rated health was significantly associated with cardiovascular risk factors and that these association were modified by sex. Second, self-rated health was not associated with cardiac disease assessed by echocardiography.

Self-rated health has previously been related to cardiovascular disease in various observational studies [21–23]. Higher self-rated health is related to a lower burden of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity), associations that persist after accounting for sociodemographic characteristics and baseline cardiac disease. Proposed mechanisms involve (i) chronic elevation of inflammatory cytokines ('immune-activated sickness') [24], (ii) an poorly balanced activation of the autonomous nervous system, and (iii) glucose levels [25]. Furthermore, self-rated health has been linked to subclinical cardiac alterations, e.g., elevated coronary artery calcium score [21], cardiac biomarkers [26], and reduced right ventricular function [27]. We found no associations with left or right ventricular echocardiographic parameters, possibly because our sample was derived from an overall healthy general population, participants were young (mean age 41 years), and echocardiographic alterations may possibly occur later in the cascade of cardiac pathology compared with elevated calcium scores and biomarkers.

Importantly, women had somewhat lower self-rated health than men, and the relationship with cardiovascular risk factors was further modified by sex. Both findings are in line with previously published data [28–30]. While the mechanisms for this remain unknown,

women may be particularly sensitive to chronic health conditions, thus affecting self-rated health [31]. Recent studies have demonstrated that the prevalence of cardiovascular disease is higher in women, emphasizing that an appraisal of sex differences is necessary to obtain maximum benefit of lifestyle interventions for the prevention of cardiac disease [32].

Throughout the last decades, quality of life has been used as a tool to measure outcome of healthcare interventions and guide healthcare policy making. Although self-rated health represents a generic measure that encompasses many dimensions of health, and as such, has limited sensitivity to address specific health issues, it is considered a reliable measure to compare health in different populations and to evaluate disease burden [33]. Because classic risk tools for cardiovascular disease do not capture social determinants, it has even been argued that self-rated health, in addition to classic risk factors, may be more useful for cardiovascular risk prediction. The EQ-5D visual analogue scale constitutes a widely used tool for this purpose [14]. In the Amazon Basin, the average self-rated health score was 75 points, which is lower compared to other studies from Brazil, where average scores of 78 to 84 points have been reported [10,34]. Notably, none of these studies were conducted in Northern Brazil, and the assessed populations were younger than our sample. In addition, differences in cultural, regional, and disease patterns may partake in understanding this difference, and further explain why general life expectancy in the Amazon Basin is below the national average in Brazil [35].

Self-rated health relies on patient-centered care, which integrates the patient's environment, values, and preferences, hence making it meaningful to the patient and the treating clinician. It is a reproducible and consistent measure across different populations

and geographical regions [33], and it may potentially complement well-established risk scoring models for cardiovascular disease [36]. Because self-rated health is easily obtained, it can help to facilitate risk assessment strategies. This is particularly important in areas such as the Amazon Basin where access to healthcare is highly variable and often limited. Considering the close relationship we found with several cardiovascular risk factors, self-rated health could be obtained by non-medical personnel and enable screening of remote communities. Consequently, selected individuals, i.e., persons with low self-rated health and no known cardiovascular risk factors, could be referred for risk factor optimization in healthcare facilities. Furthermore, it could be used as a measure for the effect of primary healthcare prevention strategies, similar to what has been reported previously [37]. Whether self-rated health is linked to clinical outcomes in the Amazon Basin, and if improvement in self-rated health could improve prognosis, should be explored in future studies.

Limitations

Socioeconomic status is associated with self-rated health and cardiovascular risk factors [38,39], and despite our multivariable adjustment, residual confounding may still exist. Health related behavior, including healthy diet and physical activity, was self-reported and this could be associated with bias. We adjusted our models for cardiac disease at baseline and in an attempt to limit reverse causation; however, some effect may persist. As no standard data values of the EQ-5D-5L have been published in Brazil, we did not apply data from the five dimensions of quality of life in this study, nor calculate index scores. Reference values for the EQ-5D-3L [10] have been published, but cross-walk datasets are

not available. To avoid the inclusion of white coat hypertension, we defined hypertension based on prior physician diagnosis and/or intake of anti-hypertensive medication.

Conclusion

Self-rated health was positively associated with a healthy lifestyle, and this relationship was modified by sex. Conversely, self-rated health was not associated with cardiac disease by echocardiography. Healthcare policies could potentially utilize self-rated health for screening or as a target to improve health behavior.

What is already known on this subject?

Self-rated health is widely used as a health indicator in various populations and provides prognostic information on mortality.

What does this study add?

In the Amazon basin self-rated health was significantly associated with cardiovascular risk factors, but not with subclinical cardiac disease by echocardiography. Assessment of self-rated health is easily obtained and could potentially be used to measure the effect of lifestyle and healthcare interventions in areas with restricted access to healthcare.

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Data availability statement

Data from the study is available upon reasonable request to the senior author. This involves de-identified participant data and statistical analyses and plans.

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Contributor statement

AEH: Conception of study, planning and design, funding, data acquisition, data analysis, statistics, writing, critical review.

LCG: Data acquisition, planning

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KOL: Data acquisition

MDK: Data analysis, critical review

MP: Critical review

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TBS: Conception of study

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PB (responsible for the overall content as guarantor): Conception of study, planning and design, funding, data acquisition, data analysis, statistics, writing, critical review.

Ethics approval statement

This study involves human participants and was approved by an Ethics Committee. Ethics committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467)

Disclosures

The authors report no conflicts of interest.

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Figure legends

Figure 1A-C

Title: Histograms of self-rated health

Legend: Distribution of self-rated health in the (A) entire study population (n=574), (B) in men (n=224) and (C) in women (n=350).

Figure 2.

Title: Forest plot

Legend: Association between self-rated health (per 10 point increase) and cardiovascular risk factors stratified by sex.

Table 1. Baseline clinical characteristics by tertiles of self-rated health

	Tertiles of self-rated health			
	1st tertile (n=231)	2nd tertile (n=226)	3rd tertile (n=117)	P trend
	0 to 70	71 to 90	91 to 100	
Baseline				
Age, years	46 ± 16	38 ± 13	39 ± 15	<0.001
Female, %	154 (67%)	127 (56%)	69 (59%)	0.06
Self-reported race, %				0.51
White	33 (14%)	24 (11%)	20 (17%)	
Mixed	163 (71%)	175 (77%)	77 (66%)	
Black	32 (14%)	26 (12%)	18 (15%)	
Indigenous	2 (1%)	1 (<1%)	1 (1%)	
BMI, kg/m^2	28 ± 6	27 ± 5	26 ± 4	0.002
Abdominal circumference, cm	90 ± 14	87 ± 12	84 ± 11	<0.001
Asthma	11 (5%)	8 (4%)	2 (2%)	0.36
COPD, %	3 (1%)	3 (1%)	1 (1%)	0.92
History of MI, %	2 (1%)	2 (1%)	1 (1%)	1.00
Heart failure, %	3 (1%)	2 (1%)	0 (0%)	0.47
Rheumatic heart disease, %	7 (3%)	7 (3%)	4 (3%)	0.97
SBP, mmHg	134 ± 20	131 ± 20	131 ± 19	0.29
DBP, mmHg	83 ± 12	81 ± 11	82 ± 12	0.17
Risk factors				
Hypertension, %	66 (29%)	32 (14%)	14 (12%)	<0.001
Hypercholesterolemia, %	52 (23%)	23 (10%)	14 (12%)	<0.001
Diabetes, %	21 (9%)	6 (3%)	6 (5%)	0.012
Obesity, %	68 (29%)	45 (20%)	20 (17%)	0.012
Smoking, %	106 (46%)	65 (29%)	46 (39%)	<0.001
Healthy diet, %	87 (38%)	130 (58%)	59 (50%)	<0.001

Physical activity, %	64 (28%)	94 (42%)	53 (45%)	<0.001
Socioeconomic status				
Work status, %				0.09
Employed	77 (33%)	98 (43%)	53 (45%)	
Self-employed	20 (9%)	23 (10%)	9 (8%)	
Other	134 (58%)	105 (47%)	55 (47%)	
Family income, BRL	1250 [800, 2000]	1500 [1000, 3000]	1200 [800, 2000]	0.11
Rural living area, %	92 (40%)	78 (35%)	55 (47%)	0.08
Biochemistry				
Blood sugar, mg/dL	110 ± 74	100 ± 27	110 ± 49	0.10
Bilirubin, mg/dL	0.40 ± 0.28	0.41 ± 0.24	0.41 ± 0.26	0.90
Platelets, mm^3	229± 76	240 ± 67	234 ± 66	0.28
Leukocytes, mm^3	6349 ± 1991	6383 ± 1723	6532 ± 1915	0.68
Reticulocytes, %	0.75 ± 0.19	0.80 ± 0.22	0.77 ± 0.22	0.44
Hemoglobin, g/dL	14 ± 1	14 ± 1	14 ± 1	0.13
C-reactive protein, mg/L	2.1 ± 8	3.1 ± 12	3.6 ± 12	0.44
Creatinine, mg/dL	0.9 [0.7, 1.0]	0.9 [0.7, 1.0]	0.8 [0.7, 1.0]	0.73
INR	1.02 ± 0.12	1.01 ± 0.10	1.02 ± 0.10	0.30
Echocardiography				
LV ejection fraction<45%, %	9 (4%)	6 (3%)	3 (3%)	0.69
LV hypertrophy, %	9 (4%)	4 (2%)	4 (3%)	0.39
Diastolic dysfunction, %	7 (3%)	5 (2%)	1 (1%)	0.43
LV ejection fraction, %	57 ± 6	57 ± 5	58 ± 5	0.48
LV mass index, g/m^2	71 ± 18	68 ± 17	70 ± 16	0.11
E/e’	7.3 ± 2.6	6.7 ± 2.1	6.9 ± 2.3	0.014
E/A	1.2 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	0.003

Left atrial volume index, mL/m^2	20 ± 6	19 ± 5	19 ± 4	0.025
TR velocity, m/s	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.2	0.34

COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, INR: international normalized ratio, LV: left ventricular, TR: tricuspid regurgitation

Table 2.
Association between self-rated health (per 10 increase), cardiovascular risk factors and disease in the entire population (n=574)

	Unadjusted odds ratio [95%CI]	P	Adjusted odds ratio [95%CI]*	P	P interaction sex
Risk factors					
Hypertension	0.77 [0.71 to 0.85]	<0.001	0.87 [0.78 to 0.97]	0.011	0.005
Hypercholesterolemia	0.83 [0.75 to 0.91]	<0.001	0.89 [0.80 to 0.99]	0.044	0.29
Diabetes	0.84 [0.73 to 0.97]	0.021	1.02 [0.86 to 1.22]	0.80	0.17
Obesity	0.90 [0.82 to 0.98]	0.017	0.95 [0.86 to 1.05]	0.30	0.78
Smoking	0.86 [0.79 to 0.93]	<0.001	0.96 [0.87 to 1.05]	0.39	0.003
Heathy diet	1.11 [1.03 to 1.20]	0.008	1.13 [1.04 to 1.24]	0.004	0.002
Physical activity	1.16 [1.06 to 1.26]	0.001	1.09 [0.99 to 1.20]	0.079	<0.001
Subclinical cardiac disease					
LV ejection fraction <45%	0.88 [0.73 to 1.08]	0.22	0.97 [0.77 to 1.23]	0.82	0.88
LV hypertrophy	0.87 [0.72 to 1.07]	0.19	0.97 [0.76 to 1.24]	0.81	0.31
Diastolic dysfunction	0.92 [0.75 to 1.15]	0.47	1.09 [0.85 to 1.40]	0.51	0.63

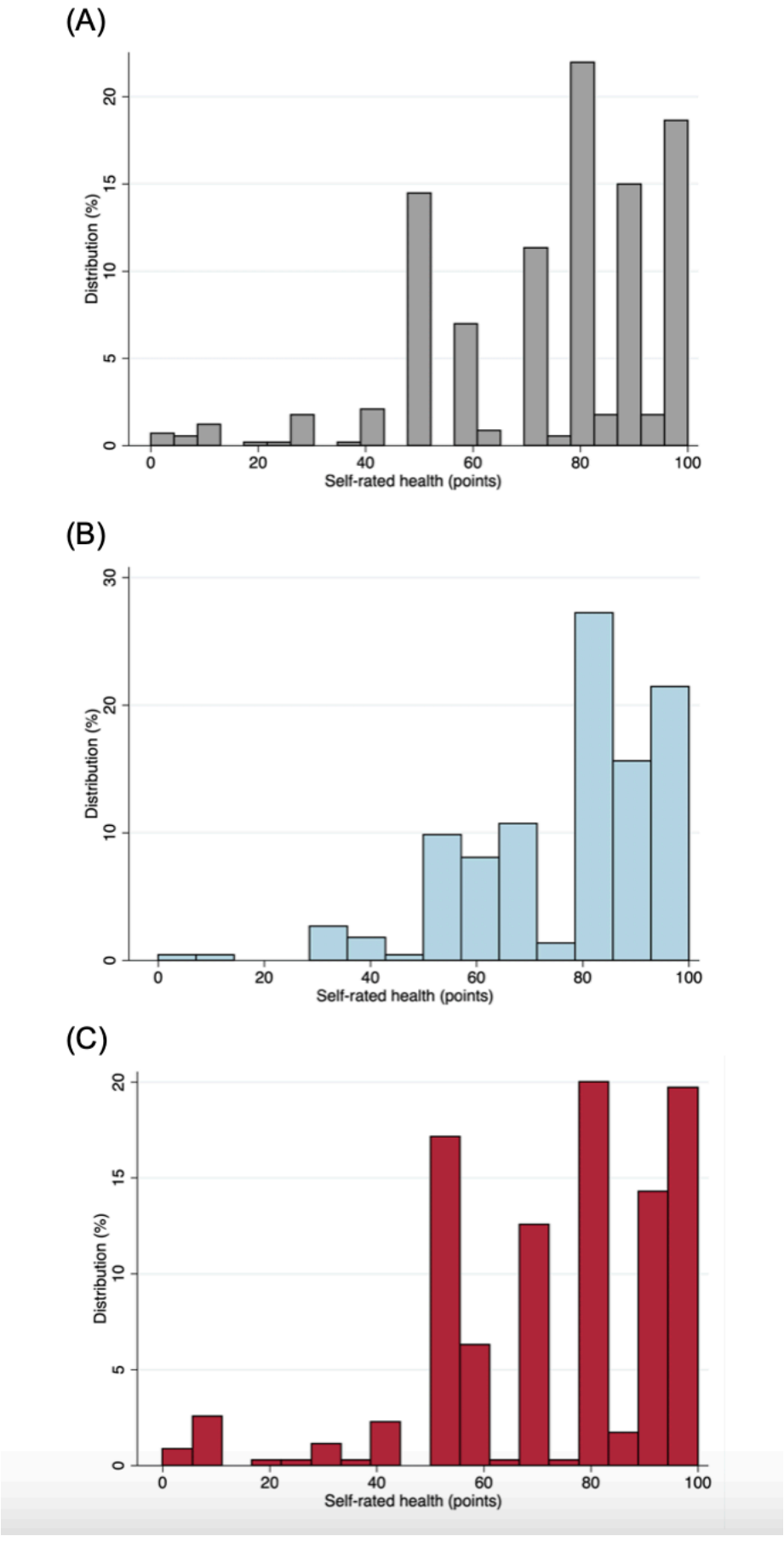
*Multivariable models were mutually adjusted other cardiovascular risk factors in addition to age, sex, work, family income, living area (rural/urban) and prior heart disease
LV: left ventricular

Table 3.
Self-rated health (per 10 point increase) and echocardiographic parameters in the entire population (n=574)

	Unadjusted beta [95%CI]	P	Adjusted beta [95%CI]*	P
Echocardiography				
Left ventricular ejection fraction	0.04 [-0.16 to 0.25]	0.67	0.04 [-0.17 to 0.25]	0.71
Left ventricular mass index	-0.46 [-1.12 to 0.21]	0.18	0.12 [-0.46 to 0.70]	0.69
e'	0.40 [0.25 to 0.54]	<0.001	0.06 [-0.04 to 0.15]	0.23
E/e'	-0.16 [-0.25 to -0.07]	0.001	0.01 [-0.07 to 0.09]	0.76
E/A	0.03 [0.02 to 0.05]	<0.001	0.01 [-0.01 to 0.01]	0.99
Left atrial volume index	-0.26 [-0.46 to -0.06]	0.012	-0.05 [-0.22 to 0.13]	0.61
Tricuspid regurgitation velocity	-0.01 [-0.02 to -0.01]	0.21	0.01 [-0.01 to 0.1]	0.95

*Multivariable models were adjusted for age, sex, work, family income, living area (rural/urban) and prior heart disease
e': mitral annular early diastolic velocity, E: early mitral inflow velocity, A; late mitral inflow velocity

Figure 1A-C


(A)
Distribution (%)
0
5
10
15
20
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20
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60
80
100
Self-rated health (points)
(B)
Distribution (%)
0
10
20
30
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20
40
60
80
100
Self-rated health (points)
(C)
Distribution (%)
0
5
10
15
20
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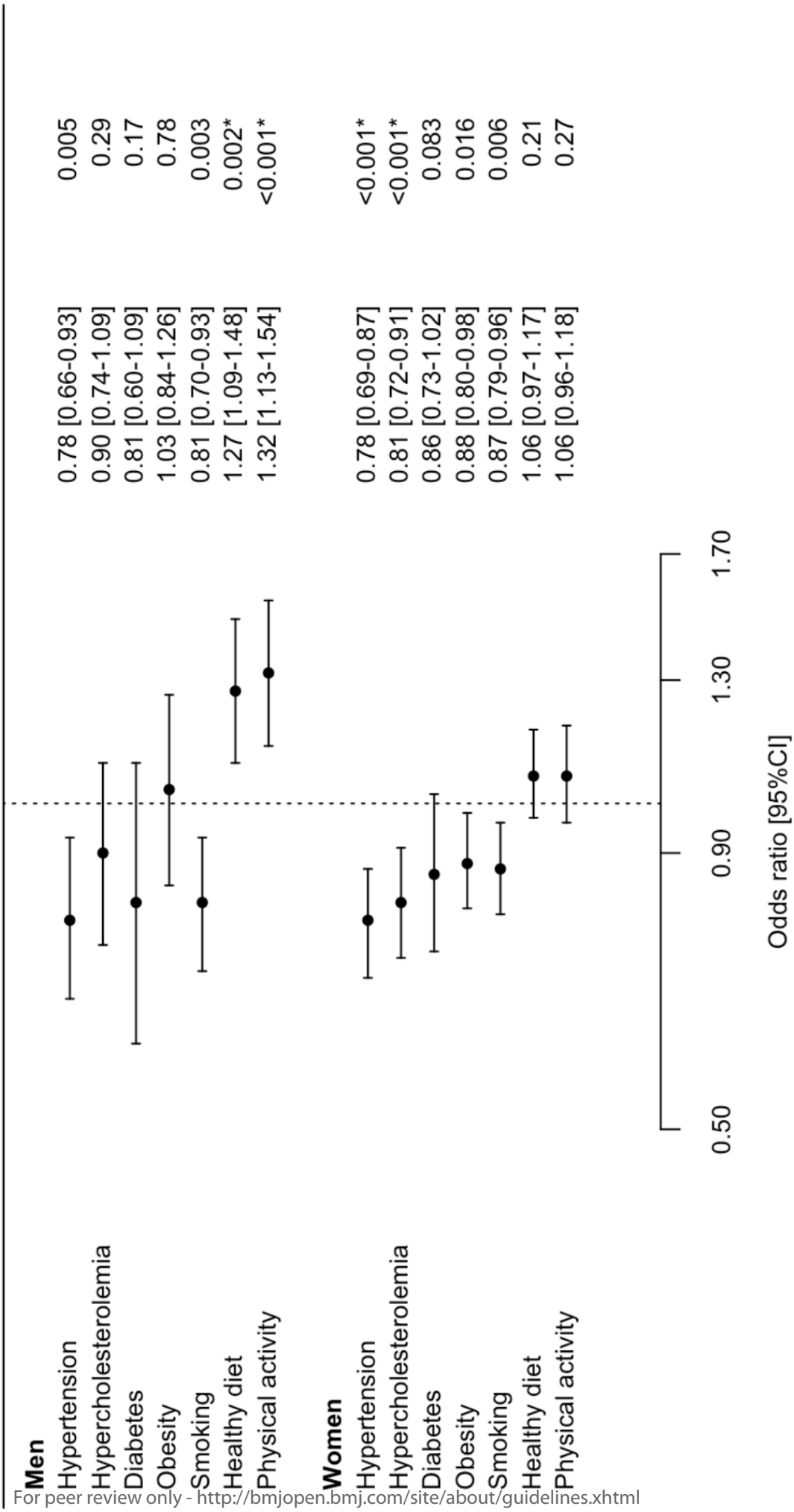
20
40
60
80
100
Self-rated health (points)

Figure 2.



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Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

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Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

Short title: Self-rated health and cardiac disease in the Amazon

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Abstract

Objective: Prior studies have suggested that self-rated health may be a useful indicator of cardiovascular disease. Consequently, we aimed to assess the relationship between self-rated health, cardiovascular risk factors, and subclinical cardiac disease in the Amazon Basin.

Setting: Cross-sectional study where self-rated health was obtained according to a visual analogue scale, ranging from 0 (poor) to 100 (excellent). We performed questionnaires, physical examination, and echocardiography. Logistic and linear regression models were applied to assess self-rated health, cardiac risk factors and cardiac disease by echocardiography. Multivariable models were mutually adjusted for other cardiovascular risk factors, clinical and socioeconomic data, and known cardiac disease.

Results: A total of 574 participants (mean age 41 years, 61% female) provided information on self-rated health (mean 75 ± 21 [interquartile range 60 to 90] points). Self-rated health (per 10-point increase) was negatively associated with hypertension (OR 0.87 [95%CI 0.78-0.97], P=0.01), hypercholesterolemia (OR 0.89 [95%CI 0.80-0.99], P=0.04) and positively with healthy diet (OR 1.13 [95%CI 1.04-1.24], P=0.004). Sex modified these associations (P-interaction<0.05) such that higher self-rated health was associated with healthy diet and physical activity in men, and lower odds of hypertension and hypercholesterolemia in women. No relationship was found with left ventricular ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P=0.22), left ventricular hypertrophy (OR 0.89 [95%CI 0.78 to 1.02], P=0.09), or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47).

Conclusion: Self-rated health was positively associated with health parameters in the Amazon Basin, but not with subclinical cardiac disease by echocardiography. Assessment

of self-rated health could be useful for screening or as a target in healthcare policies for lifestyle interventions.

Words: 265

Keywords: self-rated health; cardiovascular risk factors; echocardiography, low and middle-income countries

Article summary

Strengths and limitations

- This is the first study to examine self-rated health in a rural part of the Amazon Basin of Brazil using an internationally recognized questionnaire, EQ-5D-5L.
- We applied a state-of-the-art echocardiographic imaging protocol to identify underlying cardiovascular disease
- Self-reported health behavior could be subject to social and cultural biases
- Because no standard values of the EQ-5D-5L health instrument have been published for Brazil, it is not possible to compare our findings with other populations.
- The study design was cross-sectional.

Introduction

Cardiovascular disease is the leading cause of mortality worldwide and accounts for more than 31% of all deaths and 8% of public hospitalizations in Brazil [1,2]. Since the 1960s, Brazil has experienced a transition in health behavior and cardiovascular risk factors, where tobacco consumption has declined and obesity has increased [3]. Approximately 35% of Brazilian adults suffer from hypertension [4], the prevalence of diabetes mellitus is rising [5], and a high proportion of adults do not practice recommended levels of physical activity [1]. Differences in perception of risk factors and variability in access to healthcare unequivocally affect health behavior and the lifetime risk of cardiovascular disease. In this regard, self-rated health is widely used as a health indicator in various populations [6], is strongly associated with cardiovascular morbidity [7,8], and provides prognostic information on mortality [9]. Self-rated health and cardiovascular risk factors are also both influenced by sex [10,11]. Throughout the last decades, assessment of self-rated health has become increasingly important and is often used for healthcare surveillance and in policy making.

To understand whether self-rated health may be used to screen for cardiac disease in low-income settings, we aimed to investigate the relationship with cardiovascular risk factors and disease in the general population from the Amazon Basin of Brazil. We hypothesized that higher self-rated health is associated with less cardiovascular risk factors and disease, and that these relationships are modified by sex [12].

Methods

Study site

The study was conducted in the municipality of Cruzeiro do Sul, Acre (Northern Brazil; Amazon Basin). The prevalence for cardiovascular disease in Acre (5,815 per 100,000 inhabitants) is below the average rate for Brazil (6,025 per 100,000 inhabitants) and [2] the region is considered to be one of the poorest in Brazil and has one of the lowest population densities [13].

Patient and Public Involvement

Patients or the public were not involved in the study design, recruitment to and conduct of the study nor reporting of results. All patients were informed of the results from their own examinations conducted in the study. Data will be made available upon reasonable request to the corresponding author.

Sampling

This cross-sectional study was conducted as a part of the Malaria Heart Study (clinicaltrials.gov: NCT04445103). Participants from the general population were enrolled from June 2020 through December 2020. Through randomization, we selected 10 local healthcare clinics from Cruzeiro do Sul, equally distributed between rural and urban areas. Local healthcare agents provided lists of persons associated with each clinic from which a

random sample was invited to participate in the study. We included persons ≥18 years old who completed the examination program and responded to all questionnaires. Exclusion criteria were ongoing pregnancy, ongoing infection as assessed by examination of a medical doctor, and presence of *Plasmodium* in peripheral blood smears. A total of 504 participants were included from healthcare clinics. A second group of 70 participants from the general population who had recently completed anti-malarial treatment, and for whom the above-mentioned inclusion and exclusion criteria also applied, were included as well.

Data collection

Two different questionnaires were administered by trained interviewers (i.e., study personnel). These interviewers also filled out the questionnaires. The first was the EQ-5D-5L questionnaire which is validated in Brazilian Portuguese (study registration no.: 28276) [14]. For the purpose of this study, we used data from the EQ visual analogue scale (EQ-VAS) which provides a single estimate of self-rated health ranging from 0 to 100 points on a continuous scale. Zero represents the worst possible self-rated health and 100 represents ideal health. The second questionnaire was used to gather information about socioeconomic status, race, cardiovascular risk factors, known cardiac disease (prior myocardial infarction and heart failure), and current medications. Race was self-reported, and two persons did not answer this question. Afterwards, participants underwent a physical examination to measure height, weight, and blood pressure. Fingerstick point-of-care blood draws were used to measure glucose levels and to obtain thick and thin blood slides. Giemsa stained thick and thin blood slides were analyzed by two independent

microscopists to detect *Plasmodium*. A medical doctor (PB) evaluated all patients. None of them displayed clinical signs or symptoms of heart disease (absence of shortness of breath, chest pain, swelling of legs and irregular heart rhythm).

Cardiovascular risk factors

We assessed seven different cardiovascular risk factors. Hypertension was defined as a physician diagnosis of hypertension or intake of anti-hypertensive medication, hypercholesterolemia as a physician diagnosis of dyslipidemia or intake of lipid lowering medication, and diabetes as a physician diagnosis of diabetes or fasting blood glucose >126mg/dL [15]. Body mass index (BMI) was calculated as: body weight (kilograms)/height^2 (meters), and obesity was defined as BMI ≥30kg/m^2. Participants were classified as smokers if they were current smokers or had previously smoked. A healthy diet was defined as intake of any quantity of vegetables with a main meal ≥3 times/week. Physical activity was defined as participation in any kind of physical activity during leisure time. We did not apply any time limit or threshold.

Biochemistry

Field procedures: During examinations, we collected peripheral venous blood samples in citrate, EDTA, and serum-separator tubes, which were cooled at 2-8^{o}C. Citrate plasma was immediately separated by centrifugation (12 minutes, 3200 rpm) in a mobile laboratory and transferred to Eppendorf tubes.

Laboratory: Serum-separator tubes underwent centrifugation (10 min, 3000rpm) to extract serum which was subsequently stored at -20°C in Eppendorf tubes. Laboratory analyses were performed at Citolab and Centro de Diagnósticos, Cruzeiro do Sul, Acre, Brazil. Using EDTA blood, a complete blood count with a differential was conducted (NX-350, Sysmex, Japan; Citolab), and reticulocytes were counted manually (Citolab) [16]. Citrate plasma was used to analyze coagulation parameters (Coagmaster 2.0, Wama Diagnóstica, Brazil; Citolab). Serum was used to measure creatinine, bilirubin, and C-reactive protein (Cobas c111, Roche Diagnostics, Switzerland; Citolab and Centro de Diagnósticos). Analyses of C-reactive protein were only available in a subset of participants (n=436).

Echocardiography

A single medical doctor either performed or supervised all echocardiographic examinations (PB). Quality control was conducted on a frequent basis in a central imaging laboratory (Herlev-Gentofte Hospital, Denmark) by an investigator certified in echocardiography by the European Association of Cardiovascular Imaging. Examinations were performed bedside (Vivid-IQ, GE Healthcare, Norway), and images were stored offline for analysis in EchoPAC BT13 (v. 203.82). Analyses were conducted by AW according to contemporary guidelines [17]. Rheumatic heart disease was assessed by PB according to the World Heart Federation criteria [18]. We assessed three categories of subclinical left ventricular (LV) cardiac disease: (i) reduced contractile function defined as LV ejection fraction <45%, (ii) LV hypertrophy defined as LV mass index >115g/m^2 for men and >95g/m^2 for women and (iii) diastolic dysfunction determined according to existing guidelines [19]. Classification of diastolic dysfunction involves assessment of early and late mitral inflow

velocity, mitral annular early diastolic velocity, tricuspid regurgitation velocity and the left atrial volume index. Additional details are described in Supplemental Data 'Methods'.

Ethics

The study was approved by the institutional review committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467), local health care authorities and leaders of health care clinics. The study complies with the 2nd Declaration of Helsinki, and all patients provided written informed consent on oral and written information given in Portuguese. Illiterate participants provided fingerprints instead of signatures. For ethical reasons a medical doctor evaluated all participants on-site, and in case of suspected heart disease participants were referred to a cardiologist.

Data from the study is available upon reasonable request to the senior author. Patients or the public were not involved in the study design or reporting of results.

Statistics

Baseline characteristics for the study population were stratified according to tertiles of self-rated health (cut-offs of 70 and 91 points) and sex. Due to the nature of the distribution, tertiles of self-rated health did not contain equal amounts of participants. P for trend was calculated using linear regression models and the Cuzick nonparametric test for trend [20]. Differences between groups were compared using the chi-square test, Student's *t*-test, and the Wilcoxon rank-sum test, as appropriate. Histograms were conducted to display the distribution of self-rated health. In all statistical tests, self-rated health was treated as a continuous variable. Logistic regression models were conducted to examine the relationship between self-rated health and cardiovascular risk factors and disease.

Multivariable models were adjusted for core variables: clinical data (age, sex, race), socioeconomic data (work, family income, living area), known cardiac disease (prior myocardial infarction, heart failure, rheumatic heart disease). In addition, all associations with cardiovascular risk factors were mutually adjusted for all other risk factors. Interactions with sex were also examined. Family income was log-transformed to provide a normal distribution. The relationship between self-rated health and (i) the sum of cardiac risk factors (hypertension, hypercholesterolemia, diabetes, obesity, smoking) and (ii) echocardiographic parameters were assessed in linear regression models, which were adjusted for the core variables. All analyses were conducted in Stata v.14.2 (StataCorp, Texas, USA) and RStudio v.1.3 (R, Vienna, Austria). Two-sided P-values <0.05 were considered statistically significant.

Results

A total of 574 participants were assessed (mean age 41 ± 15 years, 61% female). Mean self-rated health was 75 ± 21 points (interquartile range 60 to 90 points) (Figure 1A). Four participants (<1%) reported 0 points, and 91 participants (16%) reported 100 points. The prevalences of cardiovascular risk factors were 20% for hypertension, 16% for hypercholesterolemia, 6% for diabetes, 23% for obesity, 38% for current or prior smoking, 52% for unhealthy diet, and 63% for absence of physical activity. Participants with lower self-rated health more frequently had all of the above risk factors and were older compared with participants with high self-rated health (P-trend<0.05; Table 1). No differences were observed in socioeconomic characteristics, biochemistry, or subclinical cardiac disease by echocardiography (reduced LV ejection fraction, hypertrophy, diastolic dysfunction) across tertiles of self-rated health (Table 1).

Cardiovascular risk factors

In unadjusted logistic regression models, better self-rated health was significantly associated with lower odds of all cardiovascular risk factors (P<0.05 for all; Table 2). In adjusted models, self-rated health (per 10-point increase) was associated with lower odds of hypertension (OR 0.87 [95%CI 0.78 to 0.97], P=0.01], hypercholesterolemia (OR 0.89 [95%CI 0.80 to 0.99], P=0.04) and higher odds of healthy diet (OR 1.13 [95%CI 1.04 to 1.24], P=0.004). In multivariable models, better self-rated health was also associated with the sum of cardiovascular risk factors (beta = -0.07 per 10-point increase [95%CI -0.10 to -0.03], P<0.001).

Subclinical cardiac disease by echocardiography

No significant associations were found between self-rated health (per 10-point increase) and subclinical cardiac disease by echocardiography: LV ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P= 0.22), LV hypertrophy (OR 0.87 [95%CI 0.72 to 1.07], P=0.19) or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47) (Table 2). No individual echocardiographic parameters were significantly associated with self-rated health in multivariable models (P>0.05 for all; Table 3).

Interactions with sex

Self-rated health was higher in men than in women (77 vs 73 points) but the difference was not statistically significant (P=0.09) (Figure 1B-C). In general, women had higher body mass index, lower income, less frequently smoked, and were more physically active compared with men (P<0.05 for all; Supplemental Table 1). Sex modified the associations with hypertension, smoking, healthy diet, and physical activity, but not cardiac disease by echocardiography (Table 2). Unadjusted associations with cardiovascular risk factors, stratified by sex, are presented in Figure 2. For men, higher self-rated health (per 10-point increase) yielded greater odds of a healthy diet (adjusted OR 1.33 [95%CI 1.12 to 1.59], P=0.002) and physical activity (adjusted OR 1.24 [95%CI 1.03 to 1.50], P=0.02). For women, higher self-rated health (per 10-point increase) was associated with lower odds of hypertension (adjusted OR 0.85 [95%CI 0.74 to 0.97], P=0.016), and hypercholesterolemia (adjusted OR 0.87 [95%CI 0.76 to 0.99], P=0.046).

Discussion

This study has two principal findings. First, in a sample of the general population from the Amazon Basin, we found that self-rated health was significantly associated with cardiovascular risk factors and that these association were modified by sex. Second, self-rated health was not associated with cardiac disease assessed by echocardiography. These findings indicate that in a low-income setting, self-rated health may to some extent provide information on cardiac risk profiles.

Self-rated health has previously been related to cardiovascular disease in various observational studies [21–23]. Higher self-rated health is related to a lower burden of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity), associations that persist after accounting for sociodemographic characteristics and baseline cardiac disease. Proposed mechanisms involve (i) chronic elevation of inflammatory cytokines ('immune-activated sickness') [24], (ii) a poorly balanced activation of the autonomous nervous system, and (iii) glucose levels [25]. Furthermore, self-rated health has been linked to subclinical cardiac alterations, e.g., elevated coronary artery calcium score [21], cardiac biomarkers [26], and reduced right ventricular function [27]. We found no associations with left or right ventricular echocardiographic parameters, possibly because our sample was derived from an overall healthy general population, participants were young (mean age 41 years), and echocardiographic alterations may possibly occur later in the cascade of cardiac pathology compared with elevated calcium scores and biomarkers.

Importantly, women had somewhat lower self-rated health than men, and the relationship with cardiovascular risk factors was further modified by sex. Both findings are in line with previously published data [28–30]. While the mechanisms for this remain unknown, women may be particularly sensitive to chronic health conditions, thus affecting self-rated health [31]. Recent studies have demonstrated that the prevalence of cardiovascular disease is higher in women, emphasizing that an appraisal of sex differences is necessary to obtain maximum benefit of lifestyle interventions for the prevention of cardiac disease [32].

Throughout the last decades, quality of life has been used as a tool to measure outcome of healthcare interventions and guide healthcare policy making. Although self-rated health represents a generic measure that encompasses many dimensions of health, and as such, has limited sensitivity to address specific health issues, it is considered a reliable measure to compare health in different populations and to evaluate disease burden [33]. Because classic risk tools for cardiovascular disease do not capture social determinants, it has even been argued that self-rated health, in addition to classic risk factors, may be more useful for cardiovascular risk prediction. The EQ-5D visual analogue scale constitutes a widely used tool for this purpose [14]. In the Amazon Basin, the average self-rated health score was 75 points, which is lower compared to other studies from Brazil, where average scores of 78 to 84 points have been reported [10,34]. Notably, none of these studies were conducted in Northern Brazil, and the assessed populations were younger than our sample. In addition, differences in cultural, regional, and disease patterns may partake in understanding this difference, and further explain why general life expectancy in the Amazon Basin is below the national average in Brazil [35].

Self-rated health relies on patient-centered care, which integrates the patient's environment, values, and preferences, hence making it meaningful to the patient and the treating clinician. It is a reproducible and consistent measure across different populations and geographical regions [33], and it may potentially complement well-established risk scoring models for cardiovascular disease [36]. Because self-rated health is easily obtained, it can help to facilitate risk assessment strategies. This is particularly important in areas such as the Amazon Basin where access to healthcare is highly variable and often limited. Considering the close relationship we found with several cardiovascular risk factors, self-rated health could be obtained by non-medical personnel and enable screening of remote communities. Consequently, selected individuals, i.e., persons with low self-rated health and no known cardiovascular risk factors, could be referred for risk factor optimization in healthcare facilities. Furthermore, it could be used as a measure for the effect of primary healthcare prevention strategies, similar to what has been reported previously [37]. Whether self-rated health is linked to clinical outcomes in the Amazon Basin, and if improvement in self-rated health could improve prognosis, should be explored in future studies.

Strengths and Limitations

Socioeconomic status is associated with self-rated health and cardiovascular risk factors [38,39], and despite our multivariable adjustment, residual confounding may still exist. Health related behavior, including healthy diet and physical activity, was self-reported and this could be associated with bias. Furthermore, it is a limitation that the questionnaire for health behavior has not been validated in other studies or settings. We adjusted our models for cardiac disease at baseline and in an attempt to limit reverse causation;

however, some effect may persist. As no standard data values of the EQ-5D-5L have been published in Brazil, we did not apply data from the five dimensions of quality of life in this study, nor calculate index scores. Data from this study represents an important first step in establishing EQ-5D-5L index values for the rural parts of the Amazon basin. Reference values for the EQ-5D-3L [10] have been published, but cross-walk datasets are not available. To avoid the inclusion of white coat hypertension, we defined hypertension based on prior physician diagnosis and/or intake of anti-hypertensive medication. While the generalizability of our findings to other regions in the world may be disputed, the Amazon Basin covers eight other countries in addition to Brazil. Hence, our findings are likely to be applicable to populations in these areas or to populations who share similar environment and culture.

Conclusion

Self-rated health was positively associated with a healthy lifestyle, and this relationship was modified by sex. Conversely, self-rated health was not associated with cardiac disease by echocardiography. Healthcare policies could potentially utilize self-rated health for screening or as a target to improve health behavior.

What is already known on this subject?

Self-rated health is widely used as a health indicator in various populations and provides prognostic information on mortality.

What does this study add?

In the Amazon basin self-rated health was significantly associated with cardiovascular risk factors, but not with subclinical cardiac disease by echocardiography. Assessment of self-rated health is easily obtained and could potentially be used to measure the effect of lifestyle and healthcare interventions in areas with restricted access to healthcare.

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Data availability statement

Data from the study is available upon reasonable request to the senior author. This involves de-identified participant data and statistical analyses and plans.

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Contributor statement

AEH: Conception of study, planning and design, funding, data acquisition, data analysis, statistics, writing, critical review.

LCG: Data acquisition, planning

AW: Data acquisition, data analysis, critical review

KOL: Data acquisition

LOM: Data acquisition

IVMV: Data acquisition

MDK: Data analysis, critical review

MP: Critical review

RMS: Expert advice

CRF: Expert advice

TBS: Conception of study

OMS: Conception of study

PB (responsible for the overall content as guarantor): Conception of study, planning and design, funding, data acquisition, data analysis, statistics, writing, critical review.

Ethics approval statement

This study involves human participants and was approved by an Ethics Committee. Ethics committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467)

Disclosures

The authors report no conflicts of interest.

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Figure legends

Figure 1A-C

Title: Histograms of self-rated health

Legend: Distribution of self-rated health in the (A) entire study population (n=574), (B) in men (n=224) and (C) in women (n=350).

Figure 2.

Title: Forest plot

Legend: Association between self-rated health (per 10 point increase) and cardiovascular risk factors stratified by sex.

Table 1. Baseline clinical characteristics by tertiles of self-rated health

	Tertiles of self-rated health			
	1st tertile (n=231)	2nd tertile (n=226)	3rd tertile (n=117)	P trend
	0 to 70	71 to 90	91 to 100	
Baseline				
Age, years	46 ± 16	38 ± 13	39 ± 15	<0.001
Female, %	154 (67%)	127 (56%)	69 (59%)	0.06
Self-reported race, %				0.51
White	33 (14%)	24 (11%)	20 (17%)	
Mixed	163 (71%)	175 (77%)	77 (66%)	
Black	32 (14%)	26 (12%)	18 (15%)	
Indigenous	2 (1%)	1 (<1%)	1 (1%)	
BMI, kg/m^2	28 ± 6	27 ± 5	26 ± 4	0.002
Abdominal circumference, cm	90 ± 14	87 ± 12	84 ± 11	<0.001
Asthma	11 (5%)	8 (4%)	2 (2%)	0.36
COPD, %	3 (1%)	3 (1%)	1 (1%)	0.92
History of MI, %	2 (1%)	2 (1%)	1 (1%)	1.00
Heart failure, %	3 (1%)	2 (1%)	0 (0%)	0.47
Rheumatic heart disease, %	7 (3%)	7 (3%)	4 (3%)	0.97
SBP, mmHg	134 ± 20	131 ± 20	131 ± 19	0.29
DBP, mmHg	83 ± 12	81 ± 11	82 ± 12	0.17
Risk factors				
Hypertension, %	66 (29%)	32 (14%)	14 (12%)	<0.001
Hypercholesterolemia, %	52 (23%)	23 (10%)	14 (12%)	<0.001
Diabetes, %	21 (9%)	6 (3%)	6 (5%)	0.012
Obesity, %	68 (29%)	45 (20%)	20 (17%)	0.012
Smoking, %	106 (46%)	65 (29%)	46 (39%)	<0.001
Healthy diet, %	87 (38%)	130 (58%)	59 (50%)	<0.001

Physical activity, %	64 (28%)	94 (42%)	53 (45%)	<0.001
Socioeconomic status				
Work status, %				0.09
Employed	77 (33%)	98 (43%)	53 (45%)	
Self-employed	20 (9%)	23 (10%)	9 (8%)	
Other	134 (58%)	105 (47%)	55 (47%)	
Family income, BRL	1250 [800, 2000]	1500 [1000, 3000]	1200 [800, 2000]	0.11
Rural living area, %	92 (40%)	78 (35%)	55 (47%)	0.08
Biochemistry				
Blood sugar, mg/dL	110 ± 74	100 ± 27	110 ± 49	0.10
Bilirubin, mg/dL	0.40 ± 0.28	0.41 ± 0.24	0.41 ± 0.26	0.90
Platelets, mm^3	229± 76	240 ± 67	234 ± 66	0.28
Leukocytes, mm^3	6349 ± 1991	6383 ± 1723	6532 ± 1915	0.68
Reticulocytes, %	0.75 ± 0.19	0.80 ± 0.22	0.77 ± 0.22	0.44
Hemoglobin, g/dL	14 ± 1	14 ± 1	14 ± 1	0.13
C-reactive protein, mg/L	2.1 ± 8	3.1 ± 12	3.6 ± 12	0.44
Creatinine, mg/dL	0.9 [0.7, 1.0]	0.9 [0.7, 1.0]	0.8 [0.7, 1.0]	0.73
INR	1.02 ± 0.12	1.01 ± 0.10	1.02 ± 0.10	0.30
Echocardiography				
LV ejection fraction<45%, %	9 (4%)	6 (3%)	3 (3%)	0.69
LV hypertrophy, %	9 (4%)	4 (2%)	4 (3%)	0.39
Diastolic dysfunction, %	7 (3%)	5 (2%)	1 (1%)	0.43
LV ejection fraction, %	57 ± 6	57 ± 5	58 ± 5	0.48
LV mass index, g/m^2	71 ± 18	68 ± 17	70 ± 16	0.11
E/e'	7.3 ± 2.6	6.7 ± 2.1	6.9 ± 2.3	0.014
E/A	1.2 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	0.003

Left atrial volume index, mL/m^2	20 ± 6	19 ± 5	19 ± 4	0.025
TR velocity, m/s	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.2	0.34

COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, INR: international normalized ratio, LV: left ventricular, TR: tricuspid regurgitation

Table 2.
Association between self-rated health (per 10 increase), cardiovascular risk factors and disease in the entire population (n=574)

	Unadjusted odds ratio [95%CI]	P	Adjusted odds ratio [95%CI]*	P	P interaction sex
Risk factors					
Hypertension	0.77 [0.71 to 0.85]	<0.001	0.87 [0.78 to 0.97]	0.011	0.005
Hypercholesterolemia	0.83 [0.75 to 0.91]	<0.001	0.89 [0.80 to 0.99]	0.044	0.29
Diabetes	0.84 [0.73 to 0.97]	0.021	1.02 [0.86 to 1.22]	0.80	0.17
Obesity	0.90 [0.82 to 0.98]	0.017	0.95 [0.86 to 1.05]	0.30	0.78
Smoking	0.86 [0.79 to 0.93]	<0.001	0.96 [0.87 to 1.05]	0.39	0.003
Heathy diet	1.11 [1.03 to 1.20]	0.008	1.13 [1.04 to 1.24]	0.004	0.002
Physical activity	1.16 [1.06 to 1.26]	0.001	1.09 [0.99 to 1.20]	0.079	<0.001
Subclinical cardiac disease					
LV ejection fraction <45%	0.88 [0.73 to 1.08]	0.22	0.97 [0.77 to 1.23]	0.82	0.88
LV hypertrophy	0.87 [0.72 to 1.07]	0.19	0.97 [0.76 to 1.24]	0.81	0.31
Diastolic dysfunction	0.92 [0.75 to 1.15]	0.47	1.09 [0.85 to 1.40]	0.51	0.63

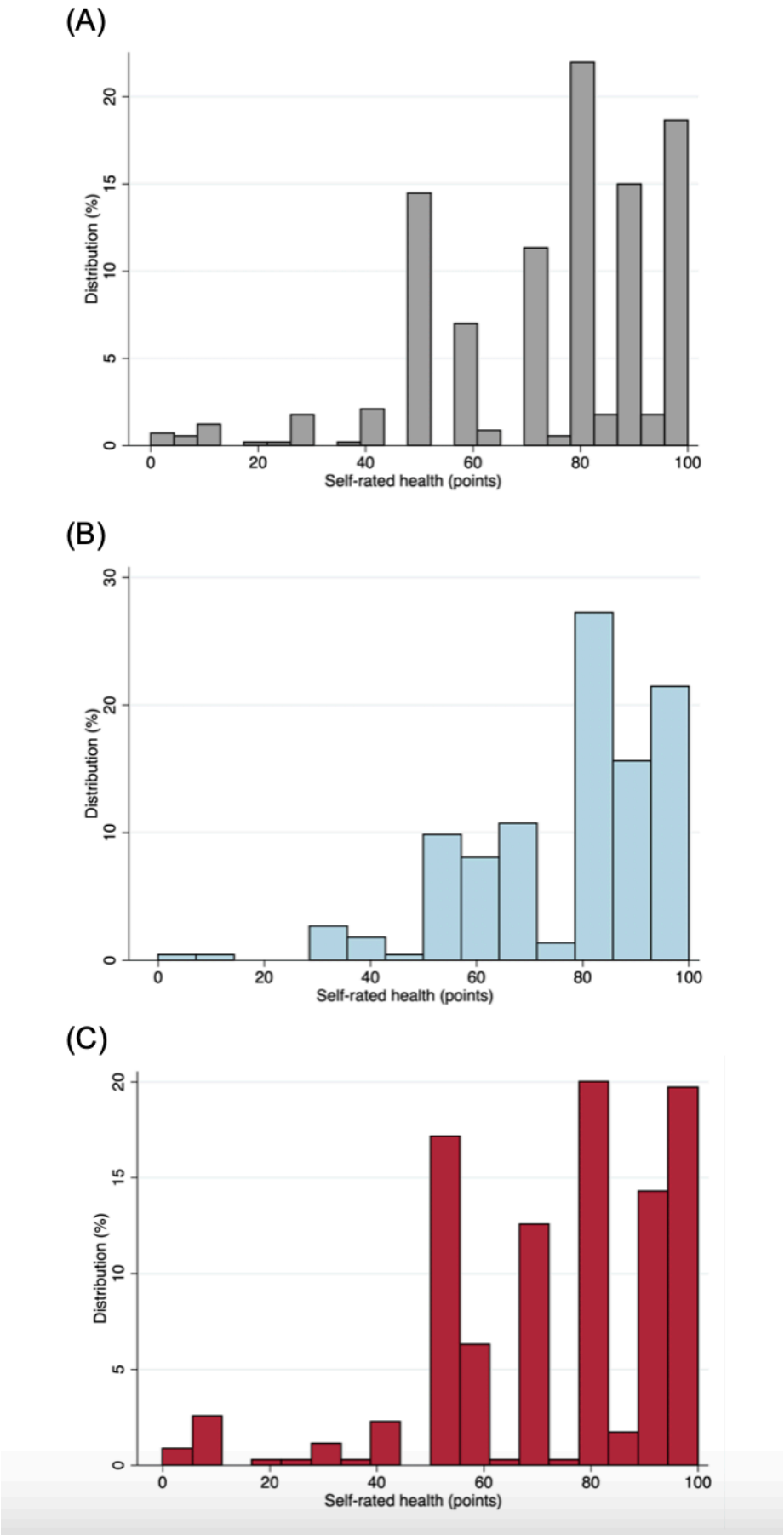
*Multivariable models were mutually adjusted other cardiovascular risk factors in addition to age, sex, work, family income, living area (rural/urban) and prior heart disease
LV: left ventricular

Table 3.
Self-rated health (per 10 point increase) and echocardiographic parameters in the entire population (n=574)

	Unadjusted beta [95%CI]	P	Adjusted beta [95%CI]*	P
Echocardiography				
Left ventricular ejection fraction	0.04 [-0.16 to 0.25]	0.67	0.04 [-0.17 to 0.25]	0.71
Left ventricular mass index	-0.46 [-1.12 to 0.21]	0.18	0.12 [-0.46 to 0.70]	0.69
e'	0.40 [0.25 to 0.54]	<0.001	0.06 [-0.04 to 0.15]	0.23
E/e'	-0.16 [-0.25 to -0.07]	0.001	0.01 [-0.07 to 0.09]	0.76
E/A	0.03 [0.02 to 0.05]	<0.001	0.01 [-0.01 to 0.01]	0.99
Left atrial volume index	-0.26 [-0.46 to -0.06]	0.012	-0.05 [-0.22 to 0.13]	0.61
Tricuspid regurgitation velocity	-0.01 [-0.02 to -0.01]	0.21	0.01 [-0.01 to 0.1]	0.95

*Multivariable models were adjusted for age, sex, work, family income, living area (rural/urban) and prior heart disease
e': mitral annular early diastolic velocity, E: early mitral inflow velocity, A; late mitral inflow velocity

Figure 1A-C


(A)
Distribution (%)
0
5
10
15
20
0
20
40
60
80
100
Self-rated health (points)
(B)
Distribution (%)
0
10
20
30
0
20
40
60
80
100
Self-rated health (points)
(C)
Distribution (%)
0
5
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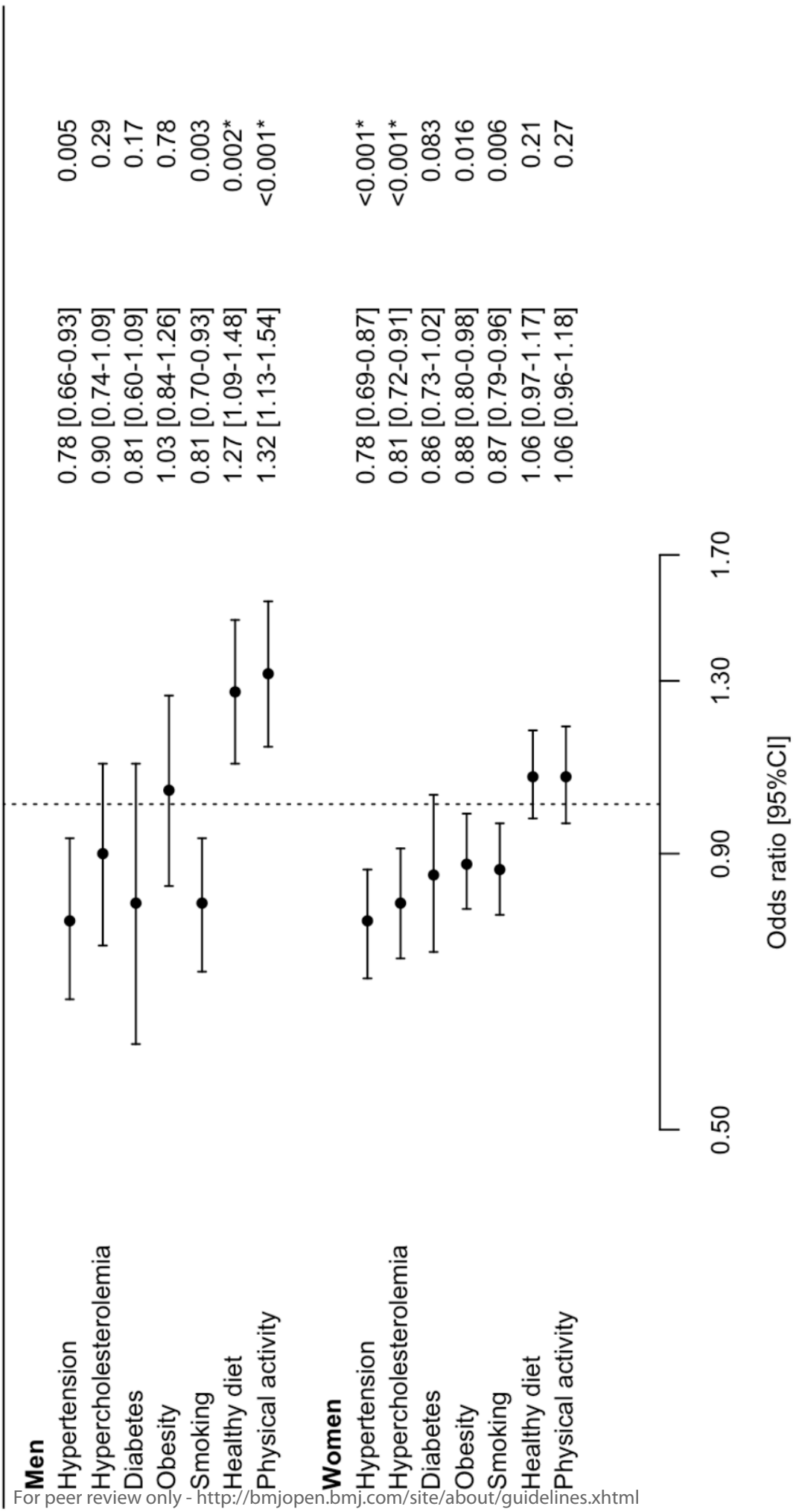
20
40
60
80
100
Self-rated health (points)

Figure 2.



Supplemental Data

Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

Anna E. Holm, MD; Laura Cordeiro Gomes; Alma Wegener, BSc; Karine O. Lima; Luan O. Matos; Isabelle V. M. Vieira; Molly D. Kaagaard; Manan Pareek, MD, PhD; Rodrigo Medeiros de Souza, PhD; Claudio Romero Farias Marinho, PhD; Tor Biering-Sørensen, MD, PhD, MPH; Odilson M. Silvestre, MD, PhD, MPH; Philip Brainin, MD, PhD

Content

Supplemental Methods: Echocardiography

End-diastolic dimensions of the left ventricle were obtained in the parasternal long axis view and measured at the level of the mitral valve leaflets. Left ventricular mass was accordingly calculated by the Devereux formula. End-diastolic and end-systolic volumes of the left ventricle were obtained in the apical two-chamber and four-chamber projections, allowing assessment of the left ventricular ejection fraction by the Simpson's biplane method. Left atrial volumes were measured by the area-length method in the same views and later divided by the body surface area to yield the left atrial volume index. In the apical four-chamber view we assessed mitral inflow velocities of early (E) and late (A) diastolic filling with pulsed wave Doppler and the deceleration time of the E-wave was measured. Pulsed wave color tissue Doppler imaging samples were placed above the septal and lateral mitral annulus to measure early diastolic velocity (e') of the left ventricle. In a focused right ventricular view, we assessed tricuspid regurgitation (TR) velocity by continuous wave doppler imaging.

Table 1. Baseline clinical characteristics by sex

	Men n=224	Women n=350	P difference
Baseline			
Age, years	40 ± 15	42 ± 15	0.28
Race, %			0.41
White	33 (15%)	44 (13%)	
Mixed	153 (68%)	262 (75%)	
Black	36 (16%)	40 (11%)	
Indigenous	1 (<1%)	3 (1%)	
BMI, kg/m^2	26 ± 4	28 ± 5	0.001
Abdominal circumference, cm	87 ± 13	88 ± 13	0.45
Asthma	4 (2%)	17 (4%)	0.06
COPD, %	2 (1%)	5 (1%)	0.57
History of MI, %	2 (1 %)	3 (1%)	0.96
Heart failure, %	3 (1%)	2 (1%)	0.33
Rheumatic heart disease, %	8 (4%)	10 (3%)	0.18
SBP, mmHg	133 ± 16	131 ± 22	0.18
DBP, mmHg	82 ± 12	82 ± 12	0.73
Risk factors			
Hypertension, %	37 (17%)	75 (21%)	0.15
Hypercholesterolemia, %	26 (12%)	63 (18%)	0.039
Diabetes, %	9 (4%)	24 (7%)	0.15
Obesity, %	31 (14%)	102 (29%)	0.001
Smoking, %	98 (44%)	119 (34%)	0.019
Healthy diet, %	99 (44%)	177 (51%)	0.14
Physical activity, %	107 (48%)	104 (30%)	0.001
Socioeconomic status			
Work status, %			0.001
Employed	70 (31%)	224 (64%)	
Self-employed	125 (56%)	103 (29%)	
Other	29 (13%)	23 (7%)	
Family income, BRL	1700 [1000, 2750]	1200 [800, 2000]	0.001
Rural living area, %	99 (44%)	126 (36%)	0.050
Biochemistry			
Blood sugar, mg/dL	100 ± 24	110 ± 67	0.047
Bilirubin, mg/dL	0.49 ± 0.32	0.35 ± 0.19	0.001
Platelets, mm^3	220 ± 81	244 ± 62	0.001
Leukocytes, mm^3	6040 ± 1590	6632 ± 2002	0.001
Reticulocytes, %	0.75 ± 0.19	0.80 ± 0.22	0.44
Hemoglobin, g/dL	15 ± 1	13 ± 1	0.001
C-reactive protein, mg/L	2.2 ± 9.6	3.2 ± 11.2	0.59
Creatinine, mg/dL	1.0 [0.8, 1.1]	0.8 [0.6, 1.0]	0.001
INR	1.03 ± 0.09	1.00 ± 0.11	0.001
Echocardiography			
LV ejection fraction<45%, %	11 (4.9%)	7 (2.0%)	0.05
LV hypertrophy, %	6 (2.7%)	11 (3.1%)	0.75
Diastolic dysfunction, %	3 (1.3%)	13 (3.7%)	0.09

COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, INR: international normalized ratio, LV: left ventricular

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	11-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12

Discussion			
Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

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Primary Subject Heading:	Global health
Secondary Subject Heading:	Cardiovascular medicine, Public health, Epidemiology
Keywords:	MENTAL HEALTH, CARDIOLOGY, PUBLIC HEALTH

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Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

Short title: Self-rated health and cardiac disease in the Amazon

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Conflicts of interest: The authors report no conflicts of interest

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Abstract

Objective: Prior studies have suggested that self-rated health may be a useful indicator of cardiovascular disease. Consequently, we aimed to assess the relationship between self-rated health, cardiovascular risk factors, and subclinical cardiac disease in the Amazon Basin.

Setting: Cross-sectional study where self-rated health was obtained according to a visual analogue scale, ranging from 0 (poor) to 100 (excellent). We performed questionnaires, physical examination, and echocardiography. Logistic and linear regression models were applied to assess self-rated health, cardiac risk factors and cardiac disease by echocardiography. Multivariable models were mutually adjusted for other cardiovascular risk factors, clinical and socioeconomic data, and known cardiac disease.

Results: A total of 574 participants (mean age 41 years, 61% female) provided information on self-rated health (mean 75 ± 21 [interquartile range 60 to 90] points). Self-rated health (per 10-point increase) was negatively associated with hypertension (OR 0.87 [95%CI 0.78-0.97], P=0.01), hypercholesterolemia (OR 0.89 [95%CI 0.80-0.99], P=0.04) and positively with healthy diet (OR 1.13 [95%CI 1.04-1.24], P=0.004). Sex modified these associations (P-interaction<0.05) such that higher self-rated health was associated with healthy diet and physical activity in men, and lower odds of hypertension and hypercholesterolemia in women. No relationship was found with left ventricular ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P=0.22), left ventricular hypertrophy (OR 0.89 [95%CI 0.78 to 1.02], P=0.09), or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47).

Conclusion: Self-rated health was positively associated with health parameters in the Amazon Basin, but not with subclinical cardiac disease by echocardiography. Our findings

are of hypothesis generating nature and future studies should aim to determine whether assessment of self-rated health may be useful for screening related to policymaking or lifestyle interventions.

Words: 275

Keywords: self-rated health; cardiovascular risk factors; echocardiography, low and middle-income countries

Article summary

Strengths and limitations

- This is the first study to examine self-rated health in a rural part of the Amazon Basin of Brazil using an internationally recognized questionnaire, EQ-5D-5L.
- We applied a state-of-the-art echocardiographic imaging protocol to identify underlying cardiovascular disease
- Self-reported health behavior could be subject to social and cultural biases
- Because no standard values of the EQ-5D-5L health instrument have been published for Brazil, it is not possible to compare our findings with other populations.
- The study design was cross-sectional.

Introduction

Cardiovascular disease is the leading cause of mortality worldwide and accounts for more than 31% of all deaths and 8% of public hospitalizations in Brazil [1,2]. Since the 1960s, Brazil has experienced a transition in health behavior and cardiovascular risk factors, where tobacco consumption has declined and obesity has increased [2]. Approximately 35% of Brazilian adults suffer from hypertension [3], the prevalence of diabetes mellitus is rising [4], and a high proportion of adults do not practice recommended levels of physical activity [2]. Differences in perception of risk factors and variability in access to healthcare unequivocally affect health behavior and the lifetime risk of cardiovascular disease. In this regard, self-rated health is widely used as a health indicator in various populations [5], is strongly associated with cardiovascular morbidity [6,7], and provides prognostic information on mortality [8]. Self-rated health and cardiovascular risk factors are also both influenced by sex [9,10]. Throughout the last decades, assessment of self-rated health has become increasingly important and is often used for healthcare surveillance and in policy making.

To understand whether self-rated health in future studies may be used to screen for cardiac disease in low-income settings, we aimed to investigate the relationship with cardiovascular risk factors and disease in the general population from the Amazon Basin of Brazil. We hypothesized that higher self-rated health is associated with less cardiovascular risk factors and disease, and that these relationships are modified by sex [11].

Methods

Study site

The study was conducted in the municipality of Cruzeiro do Sul, Acre (Northern Brazil; Amazon Basin). The prevalence for cardiovascular disease in Acre (5,815 per 100,000 inhabitants) is below the average rate for Brazil (6,025 per 100,000 inhabitants) and [12] the region is considered to be one of the poorest in Brazil and has one of the lowest population densities [13].

Patient and Public Involvement

Patients or the public were not involved in the study design, recruitment to and conduct of the study nor reporting of results. All patients were informed of the results from their own examinations conducted in the study. Data will be made available upon reasonable request to the corresponding author.

Sampling

This cross-sectional study was conducted as a part of the Malaria Heart Study (clinicaltrials.gov: NCT04445103). Participants from the general population were enrolled from June 2020 through December 2020. Through randomization, we selected 10 local healthcare clinics from Cruzeiro do Sul, equally distributed between rural and urban areas. Local healthcare agents provided lists of persons associated with each clinic, who we invited to participate in the study (Figure 1). We included persons ≥18 years old who

completed the examination program and responded to all questionnaires. Exclusion criteria were ongoing pregnancy, ongoing infection as assessed by examination of a medical doctor, and presence of *Plasmodium* in peripheral blood smears. A total of 504 participants from the general population were included from healthcare clinics. As a part of the main study, we also examined patients diagnosed with uncomplicated malaria in healthcare clinics. This group of participants underwent a follow-up examination a median of 30 days later, when they had completed treatment and had no symptoms of malaria. According to the above-mentioned inclusion and exclusion criteria, a total of 70 participants from this group were eligible for inclusion (Figure 1).

Data collection

Two different questionnaires were administered by trained interviewers (i.e., study personnel). These interviewers also filled out the questionnaires. The first was the EQ-5D-5L questionnaire which is validated in Brazilian Portuguese (study registration no.: 28276) [14]. For the purpose of this study, we used data from the EQ visual analogue scale (EQ-VAS) which provides a single estimate of self-rated health ranging from 0 to 100 points on a continuous scale. Zero represents the worst possible self-rated health and 100 represents ideal health. The second questionnaire was used to gather information about socioeconomic status, race, cardiovascular risk factors, known cardiac disease (prior myocardial infarction and heart failure), and current medications. Race was self-reported, and two persons did not answer this question. Afterwards, participants underwent a physical examination to measure height, weight, and blood pressure. Fingerstick point-of-care blood draws were used to measure glucose levels and to obtain thick and thin blood

slides. Giemsa stained thick and thin blood slides were analyzed by two independent microscopists to detect *Plasmodium*. A medical doctor (PB) evaluated all patients. None of them displayed clinical signs or symptoms of heart disease (absence of shortness of breath, chest pain, swelling of legs and irregular heart rhythm). All data was quality controlled by PB on a daily basis.

Cardiovascular risk factors

We assessed seven different cardiovascular risk factors. Hypertension was defined as a physician diagnosis of hypertension or intake of anti-hypertensive medication, hypercholesterolemia as a physician diagnosis of dyslipidemia or intake of lipid lowering medication, and diabetes as a physician diagnosis of diabetes or fasting blood glucose >126mg/dL [15]. Body mass index (BMI) was calculated as: body weight (kilograms)/height^2 (meters), and obesity was defined as BMI ≥30kg/m^2. Participants were classified as smokers if they were current smokers or had previously smoked. A healthy diet was defined as intake of any quantity of vegetables with a main meal ≥3 times/week. Physical activity was defined as participation in any kind of physical activity, on a weekly basis, during leisure time. We did not apply any time limit or threshold.

Biochemistry

Field procedures: During examinations, we collected peripheral venous blood samples in citrate, EDTA, and serum-separator tubes, which were cooled at 2-8°C. Citrate plasma was immediately separated by centrifugation (12 minutes, 3200 rpm) in a mobile laboratory and transferred to Eppendorf tubes.

Laboratory: Serum-separator tubes underwent centrifugation (10 min, 3000rpm) to extract serum which was subsequently stored at -20°C in Eppendorf tubes. Laboratory analyses were performed at Citolab and Centro de Diagnósticos, Cruzeiro do Sul, Acre, Brazil. Using EDTA blood, a complete blood count with a differential was conducted (NX-350, Sysmex, Japan; Citolab), and reticulocytes were counted manually (Citolab) [16]. Citrate plasma was used to analyze coagulation parameters (Coagmaster 2.0, Wama Diagnóstica, Brazil; Citolab). Serum was used to measure creatinine, bilirubin, and C-reactive protein (Cobas c111, Roche Diagnostics, Switzerland; Citolab and Centro de Diagnósticos). Analyses of C-reactive protein were only available in a subset of participants (n=436).

Echocardiography

A single medical doctor either performed or supervised all echocardiographic examinations (PB). Quality control was conducted on a frequent basis in a central imaging laboratory (Herlev-Gentofte Hospital, Denmark) by an investigator certified in echocardiography by the European Association of Cardiovascular Imaging. Examinations were performed bedside (Vivid-IQ, GE Healthcare, Norway), and images were stored offline for analysis in EchoPAC BT13 (v. 203.82). Analyses were conducted by AW according to contemporary guidelines [17]. Rheumatic heart disease was assessed by PB according to the World Heart Federation criteria [18]. We assessed three categories of subclinical left ventricular

(LV) cardiac disease: (i) reduced contractile function defined as LV ejection fraction <45%, (ii) LV hypertrophy defined as LV mass index >115g/m^2 for men and >95g/m^2 for women and (iii) diastolic dysfunction determined according to existing guidelines [19]. Classification of diastolic dysfunction involves assessment of early and late mitral inflow velocity, mitral annular early diastolic velocity, tricuspid regurgitation velocity and the left atrial volume index. Additional details are described in Supplemental Data 'Methods'.

Ethics

The study was approved by the institutional review committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467), local health care authorities and leaders of health care clinics. The study complies with the 2nd Declaration of Helsinki, and all patients provided written informed consent on oral and written information given in Portuguese. Illiterate participants provided fingerprints instead of signatures. For ethical reasons a medical doctor evaluated all participants on-site, and in case of suspected heart disease participants were referred to a cardiologist.
Data from the study is available upon reasonable request to the senior author. Patients or the public were not involved in the study design or reporting of results.

Statistics

Baseline characteristics for the study population were stratified according to tertiles of self-rated health (cut-offs of 70 and 91 points) and sex. Due to the nature of the distribution, tertiles of self-rated health did not contain equal amounts of participants. P for trend was calculated using linear regression models and the Cuzick nonparametric test for trend [20]. Differences between groups were compared using the chi-square test, Student's *t*-test,

and the Wilcoxon rank-sum test, as appropriate. Histograms were conducted to display the distribution of self-rated health. In all statistical tests, self-rated health was treated as a continuous variable. Logistic regression models were conducted to examine the relationship between self-rated health and cardiovascular risk factors and disease. Multivariable models were adjusted for core variables: clinical data (age, sex, race), socioeconomic data (work, family income, living area), known cardiac disease (prior myocardial infarction, heart failure, rheumatic heart disease). Included variables were selected based on prior studies of self-rated health [21–23] and were defined prior to commencing data analyses. In addition, all associations with cardiovascular risk factors were mutually adjusted for all other risk factors. Interactions with sex were also examined. Family income was log-transformed to provide a normal distribution. The relationship between self-rated health and (i) the sum of cardiac risk factors (hypertension, hypercholesterolemia, diabetes, obesity, smoking) and (ii) echocardiographic parameters were assessed in linear regression models, which were adjusted for the core variables. As this was a secondary study, no sample size calculation was conducted. All analyses were conducted in Stata v.14.2 (StataCorp, Texas, USA) and RStudio v.1.3 (R, Vienna, Austria). Two-sided P-values <0.05 were considered statistically significant.

Results

A total of 574 participants were assessed (mean age 41 ± 15 years, 61% female). Mean self-rated health was 75 ± 21 points (interquartile range 60 to 90 points) (Figure 2A). Four participants (<1%) reported 0 points, and 91 participants (16%) reported 100 points. The prevalences of cardiovascular risk factors were 20% for hypertension, 16% for hypercholesterolemia, 6% for diabetes, 23% for obesity, 38% for current or prior smoking, 52% for unhealthy diet, and 63% for absence of physical activity. Participants with lower self-rated health more frequently had all of the above risk factors and were older compared with participants with high self-rated health (P-trend<0.05; Table 1). No differences were observed in socioeconomic characteristics, biochemistry, or subclinical cardiac disease by echocardiography (reduced LV ejection fraction, hypertrophy, diastolic dysfunction) across tertiles of self-rated health (Table 1).

Cardiovascular risk factors

In unadjusted logistic regression models, better self-rated health was significantly associated with lower odds of all cardiovascular risk factors (P<0.05 for all; Table 2). In adjusted models, self-rated health (per 10-point increase) was associated with lower odds of hypertension (OR 0.87 [95%CI 0.78 to 0.97], P=0.01], hypercholesterolemia (OR 0.89 [95%CI 0.80 to 0.99], P=0.04) and higher odds of healthy diet (OR 1.13 [95%CI 1.04 to 1.24], P=0.004). In multivariable models, better self-rated health was also associated with the sum of cardiovascular risk factors (beta = -0.07 per 10-point increase [95%CI -0.10 to -0.03], P<0.001). The associations remained unchanged when we excluded participants recently treated for malaria (Supplemental Table 1 and Supplemental Figure 1).

Subclinical cardiac disease by echocardiography

No significant associations were found between self-rated health (per 10-point increase) and subclinical cardiac disease by echocardiography: LV ejection fraction<45% (OR 0.88 [95%CI 0.73 to 1.08], P= 0.22), LV hypertrophy (OR 0.87 [95%CI 0.72 to 1.07], P=0.19) or diastolic dysfunction (OR 0.92 [95%CI 0.75 to 1.15], P=0.47) (Table 2). No individual echocardiographic parameters were significantly associated with self-rated health in multivariable models (P>0.05 for all; Table 3).

Interactions with sex

Self-rated health was higher in men than in women (77 vs 73 points) but the difference was not statistically significant (P=0.09) (Figure 2B-C). In general, women had higher body mass index, lower income, less frequently smoked, and were less physically active compared with men (P<0.05 for all; Supplemental Table 2). Sex modified the associations with hypertension, smoking, healthy diet, and physical activity, but not cardiac disease by echocardiography (Table 2). Unadjusted associations with cardiovascular risk factors, stratified by sex, are presented in Figure 3. For men, higher self-rated health (per 10-point increase) yielded greater odds of a healthy diet (adjusted OR 1.33 [95%CI 1.12 to 1.59], P=0.002) and physical activity (adjusted OR 1.24 [95%CI 1.03 to 1.50], P=0.02). For women, higher self-rated health (per 10-point increase) was associated with lower odds of hypertension (adjusted OR 0.85 [95%CI 0.74 to 0.97], P=0.016), and hypercholesterolemia (adjusted OR 0.87 [95%CI 0.76 to 0.99], P=0.046). The associations remained unchanged when we excluded participants from the malaria group (Supplemental Table 2 and Supplemental Figure 1).

Discussion

This study has two principal findings. First, in a sample of the general population from the Amazon Basin, we found that self-rated health was significantly associated with cardiovascular risk factors and that these association were modified by sex. Second, self-rated health was not associated with cardiac disease assessed by echocardiography. These findings indicate that in a low-income setting, self-rated health may to some extent provide information on cardiac risk profiles.

Self-rated health has previously been related to cardiovascular disease in various observational studies [24–26]. Higher self-rated health is related to a lower burden of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity), associations that persist after accounting for sociodemographic characteristics and baseline cardiac disease. Proposed mechanisms involve (i) chronic elevation of inflammatory cytokines ('immune-activated sickness') [27], (ii) a poorly balanced activation of the autonomous nervous system, and (iii) glucose levels [28]. Furthermore, self-rated health has been linked to subclinical cardiac alterations, e.g., elevated coronary artery calcium score [24], cardiac biomarkers [29], and reduced right ventricular function [30]. We found no associations with left or right ventricular echocardiographic parameters, possibly because our sample was derived from an overall healthy general population, participants were young (mean age 41 years), and echocardiographic alterations may possibly occur later in the cascade of cardiac pathology compared with elevated calcium scores and biomarkers. Another potential reason could be low statistical power due to the limited size of the study population.

Importantly, women had somewhat lower self-rated health than men, and the relationship with cardiovascular risk factors was further modified by sex. Both findings are in line with previously published data [31–33]. While the mechanisms for this remain unknown, women may be particularly sensitive to chronic health conditions, thus affecting self-rated health [34]. Recent studies have demonstrated that the prevalence of cardiovascular disease is higher in women, emphasizing that an appraisal of sex differences is necessary to obtain maximum benefit of lifestyle interventions for the prevention of cardiac disease [35].

Throughout the last decades, quality of life has been used as a tool to measure outcome of healthcare interventions and guide healthcare policy making. Although self-rated health represents a generic measure that encompasses many dimensions of health, and as such, has limited sensitivity to address specific health issues, it is considered a reliable measure to compare health in different populations and to evaluate disease burden [36]. Because classic risk tools for cardiovascular disease do not capture social determinants, it has even been argued that self-rated health, in addition to classic risk factors, may be more useful for cardiovascular risk prediction. The EQ-5D visual analogue scale constitutes a widely used tool for this purpose [14]. In the Amazon Basin, the average self-rated health score was 75 points, which is lower compared to other studies from Brazil, where average scores of 78 to 84 points have been reported [9,37]. Notably, none of these studies were conducted in Northern Brazil, and the assessed populations were younger than our sample. In addition, differences in cultural, regional, and disease patterns may partake in understanding this difference, and further explain why general life expectancy in the Amazon Basin is below the national average in Brazil [38].

Self-rated health relies on patient-centered care, which integrates the patient's environment, values, and preferences, hence making it meaningful to the patient and the treating clinician. It is a reproducible and consistent measure across different populations and geographical regions [36], and it may potentially complement well-established risk scoring models for cardiovascular disease [39]. Because self-rated health is easily obtained, it can help to facilitate risk assessment strategies. This is particularly important in areas such as the Amazon Basin where access to healthcare is highly variable and often limited. Considering the close relationship we found with several cardiovascular risk factors, self-rated health could be obtained by non-medical personnel and enable screening of remote communities. Consequently, selected individuals, i.e., persons with low self-rated health and no known cardiovascular risk factors, could be referred for risk factor optimization in healthcare facilities. Furthermore, it could be used as a measure for the effect of primary healthcare prevention strategies, similar to what has been reported previously [40]. Whether self-rated health is linked to clinical outcomes in the Amazon Basin, and if improvement in self-rated health could improve prognosis, should be explored in future studies.

Strengths and Limitations

Socioeconomic status is perceived to be associated with self-rated health and cardiovascular risk factors [41,42], and despite our multivariable adjustment, residual confounding may still exist. Interestingly, parameters of socioeconomic status did not vary significantly across tertiles of self-reported health (Table 1), indicating that this relationship may differ in this region. Health related behavior, including healthy diet and physical activity, was self-reported and this could be associated with bias. Furthermore, it is a

limitation that the questionnaire for health behavior has not been validated in other studies or settings. We adjusted our models for cardiac disease at baseline in an attempt to limit reverse causation; however, some effect may persist. To reduce bias, we had a clear and predefined hypothesis prior to commencing data analyses and a rigorous design for the sequence of questionnaires. To increase the sample size, we included a subgroup of participants recently treated for malaria (n=70). As this group was derived from the same population, had no symptoms of malaria and all associations remained significant when excluded, we do not believe its inclusion affects the generalizability of our results. Because no standard data values of the EQ-5D-5L have been published in Brazil, we did not apply data from the five dimensions of quality of life in this study, nor calculate index scores. Data from this study represents an important first step in establishing EQ-5D-5L index values for the rural parts of the Amazon basin. Reference values for the EQ-5D-3L [9] have been published, but cross-walk datasets are not available. To avoid the inclusion of white coat hypertension, we defined hypertension based on prior physician diagnosis and/or intake of anti-hypertensive medication. While the generalizability of our findings to other regions in the world may be disputed, the Amazon Basin covers eight other countries in addition to Brazil. Hence, our findings are likely to be applicable to populations in these areas or to populations who share similar environment and culture.

Conclusion

Self-rated health was positively associated with a healthy lifestyle, and this relationship was modified by sex. Conversely, self-rated health was not associated with cardiac disease by echocardiography. On a hypothesis-generating basis, healthcare policies could

potentially utilize self-rated health for screening or as a target to improve health behavior. Nevertheless, this should be investigated in future validation studies.

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Data availability statement

Data from the study is available upon reasonable request to the senior author. This involves de-identified participant data and statistical analyses and plans.

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Contributor statement

AEH, TBS, OMS and PB were responsible for the conception of the study and research question. AEH and PB acquired funding to conduct the study. AEH, LCG and PB planned

the study and facilitated logistics. AEH, LCG, LOM AW, KOL, IVMV, PB collected data from the field and prepared collected samples in the laboratory. AEH, AW, MDK and PB undertook data analyses while AEH conducted statistical analyses and wrote the manuscript with support from PB. MP, RMS and CRF provided critical feedback for interpretation of the data. All authors critically reviewed the study findings and read and approved the final version before submission. PB is responsible for the overall content as guarantor.

Ethics approval statement

This study involves human participants and was approved by an Ethics Committee. Ethics committee at Federal University of Acre and University of São Paulo (CAAE: 26552619.6.0000.510 and 32947520.4.0000.5467)

Disclosures

The authors report no conflicts of interest.

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Figure legends

Figure 1.

Title: Flowchart

Legend: Inclusion of the study population in Cruzeiro do Sul, Acre.

Figure 2A-C.

Title: Histograms of self-rated health

Legend: Distribution of self-rated health in the (A) entire study population (n=574), (B) in men (n=224) and (C) in women (n=350).

Figure 3.

Title: Forest plot

Legend: Association between self-rated health (per 10 point increase) and cardiovascular risk factors stratified by sex. * indicates that the association persisted to be significant in multivariable models.

Table 1. Baseline clinical characteristics by tertiles of self-rated health

	Tertiles of self-rated health			
	1st tertile (n=231)	2nd tertile (n=226)	3rd tertile (n=117)	P trend*
	0 to 70	71 to 90	91 to 100	
Baseline				
Age, years	46 ± 16	38 ± 13	39 ± 15	<0.001
Female, %	154 (67%)	127 (56%)	69 (59%)	0.06
Self-reported race, %				0.51
White	33 (14%)	24 (11%)	20 (17%)	
Mixed	163 (71%)	175 (77%)	77 (66%)	
Black	32 (14%)	26 (12%)	18 (15%)	
Indigenous	2 (1%)	1 (<1%)	1 (1%)	
BMI, kg/m^2	28 ± 6	27 ± 5	26 ± 4	0.002
Abdominal circumference, cm	90 ± 14	87 ± 12	84 ± 11	<0.001
Asthma	11 (5%)	8 (4%)	2 (2%)	0.36
COPD, %	3 (1%)	3 (1%)	1 (1%)	0.92
History of MI, %	2 (1%)	2 (1%)	1 (1%)	1.00
Heart failure, %	3 (1%)	2 (1%)	0 (0%)	0.47
Rheumatic heart disease, %	7 (3%)	7 (3%)	4 (3%)	0.97
SBP, mmHg	134 ± 20	131 ± 20	131 ± 19	0.29
DBP, mmHg	83 ± 12	81 ± 11	82 ± 12	0.17
Risk factors				
Hypertension, %	66 (29%)	32 (14%)	14 (12%)	<0.001
Hypercholesterolemia, %	52 (23%)	23 (10%)	14 (12%)	<0.001
Diabetes, %	21 (9%)	6 (3%)	6 (5%)	0.012
Obesity, %	68 (29%)	45 (20%)	20 (17%)	0.012
Smoking, %	106 (46%)	65 (29%)	46 (39%)	<0.001

Healthy diet, %	87 (38%)	130 (58%)	59 (50%)	<0.001
Physical activity, %	64 (28%)	94 (42%)	53 (45%)	<0.001
Socioeconomic status				
Work status, %				0.09
Employed	77 (33%)	98 (43%)	53 (45%)	
Self-employed	20 (9%)	23 (10%)	9 (8%)	
Other	134 (58%)	105 (47%)	55 (47%)	
Family income, BRL	1250 [800, 2000]	1500 [1000, 3000]	1200 [800, 2000]	0.11
Rural living area, %	92 (40%)	78 (35%)	55 (47%)	0.08
Biochemistry				
Blood sugar, mg/dL	110 ± 74	100 ± 27	110 ± 49	0.10
Bilirubin, mg/dL	0.3 [0.2, 0.5]	0.4 [0.2, 0.5]	0.4 [0.2, 0.5]	0.55
Platelets, mm^3	229± 76	240 ± 67	234 ± 66	0.28
Leukocytes, mm^3	6349 ± 1991	6383 ± 1723	6532 ± 1915	0.68
Reticulocytes, %	0.75 ± 0.19	0.80 ± 0.22	0.77 ± 0.22	0.44
Hemoglobin, g/dL	14 ± 1	14 ± 1	14 ± 1	0.13
C-reactive protein, mg/L	0 [0, 0]	0 [0, 0]	0 [0, 0]	0.44
Creatinine, mg/dL	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.59
INR	1.02 ± 0.12	1.01 ± 0.10	1.02 ± 0.10	0.30
Echocardiography				
LV ejection fraction<45%, %	9 (4%)	6 (3%)	3 (3%)	0.69
LV hypertrophy, %	9 (4%)	4 (2%)	4 (3%)	0.39
Diastolic dysfunction, %	7 (3%)	5 (2%)	1 (1%)	0.43
LV ejection fraction, %	57 ± 6	57 ± 5	58 ± 5	0.48
LV mass index, g/m^2	71 ± 18	68 ± 17	70 ± 16	0.11
E/e'	7.3 ± 2.6	6.7 ± 2.1	6.9 ± 2.3	0.014

E/A	1.2 ± 0.5	1.3 ± 0.4	1.3 ± 0.4	0.003
Left atrial volume index, mL/m^2	20 ± 6	19 ± 5	19 ± 4	0.025
TR velocity, m/s	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.2	0.34

COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, INR: international normalized ratio, LV: left ventricular, TR: tricuspid regurgitation
*P for trend was calculated using linear regression models for normally distributed variables and Cuzick's nonparametric test for trend for non-normally distributed variables.
Normally distributed variables are displayed as mean ± standard deviation.
Non-normally distributed variables are presented as median [interquartile range].
Proportions are displayed as n (%).

Table 2.
Association between self-rated health (per 10 increase), cardiovascular risk factors and disease in the entire population (n=574)

	Unadjusted odds ratio [95%CI]	P	Adjusted odds ratio [95%CI]*	P	P interaction sex
Risk factors					
Hypertension	0.77 [0.71 to 0.85]	<0.001	0.87 [0.78 to 0.97]	0.011	0.005
Hypercholesterolemia	0.83 [0.75 to 0.91]	<0.001	0.89 [0.80 to 0.99]	0.044	0.29
Diabetes	0.84 [0.73 to 0.97]	0.021	1.02 [0.86 to 1.22]	0.80	0.17
Obesity	0.90 [0.82 to 0.98]	0.017	0.95 [0.86 to 1.05]	0.30	0.78
Smoking	0.86 [0.79 to 0.93]	<0.001	0.96 [0.87 to 1.05]	0.39	0.003
Heathy diet	1.11 [1.03 to 1.20]	0.008	1.13 [1.04 to 1.24]	0.004	0.002
Physical activity	1.16 [1.06 to 1.26]	0.001	1.09 [0.99 to 1.20]	0.079	<0.001
Subclinical cardiac disease					
LV ejection fraction <45%	0.88 [0.73 to 1.08]	0.22	0.97 [0.77 to 1.23]	0.82	0.88
LV hypertrophy	0.87 [0.72 to 1.07]	0.19	0.97 [0.76 to 1.24]	0.81	0.31
Diastolic dysfunction	0.92 [0.75 to 1.15]	0.47	1.09 [0.85 to 1.40]	0.51	0.63

*Multivariable models were mutually adjusted for cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity, smoking, healthy diet, physical activity) in addition to age, sex, work, family income, living area (rural/urban) and prior heart disease
LV: left ventricular

Table 3.
Self-rated health (per 10 point increase) and echocardiographic parameters in the entire population (n=574)

	Unadjusted beta [95%CI]	P	Adjusted beta [95%CI]*	P
Echocardiography				
Left ventricular ejection fraction	0.04 [-0.16 to 0.25]	0.67	0.04 [-0.17 to 0.25]	0.71
Left ventricular mass index	-0.46 [-1.12 to 0.21]	0.18	0.12 [-0.46 to 0.70]	0.69
e'	0.40 [0.25 to 0.54]	<0.001	0.06 [-0.04 to 0.15]	0.23
E/e'	-0.16 [-0.25 to -0.07]	0.001	0.01 [-0.07 to 0.09]	0.76
E/A	0.03 [0.02 to 0.05]	<0.001	0.01 [-0.01 to 0.01]	0.99
Left atrial volume index	-0.26 [-0.46 to -0.06]	0.012	-0.05 [-0.22 to 0.13]	0.61
Tricuspid regurgitation velocity	-0.01 [-0.02 to -0.01]	0.21	0.01 [-0.01 to 0.1]	0.95

*Multivariable models were adjusted for age, sex, work, family income, living area (rural/urban) and prior heart disease
e': mitral annular early diastolic velocity, E: early mitral inflow velocity, A; late mitral inflow velocity

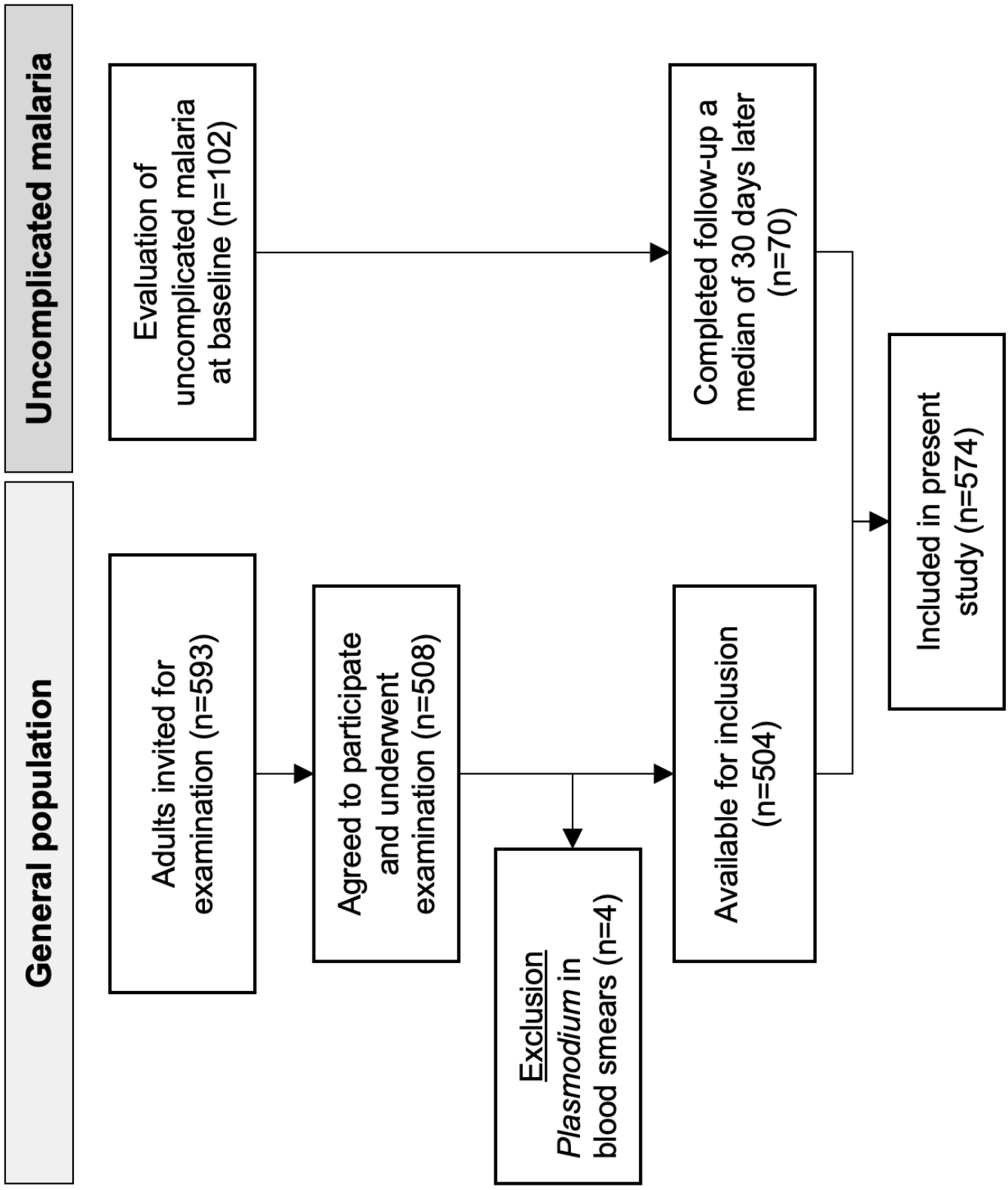

Uncomplicated malaria
General population
Evaluation of uncomplicated malaria at baseline (n=102)
Completed follow-up a median of 30 days later (n=70)
Adults invited for examination (n=593)
Agreed to participate and underwent examination (n=508)
Exclusion Plasmodium in blood smears (n=4)
Available for inclusion (n=504)
Included in present study (n=574)

Figure 1.

Figure 2A-C

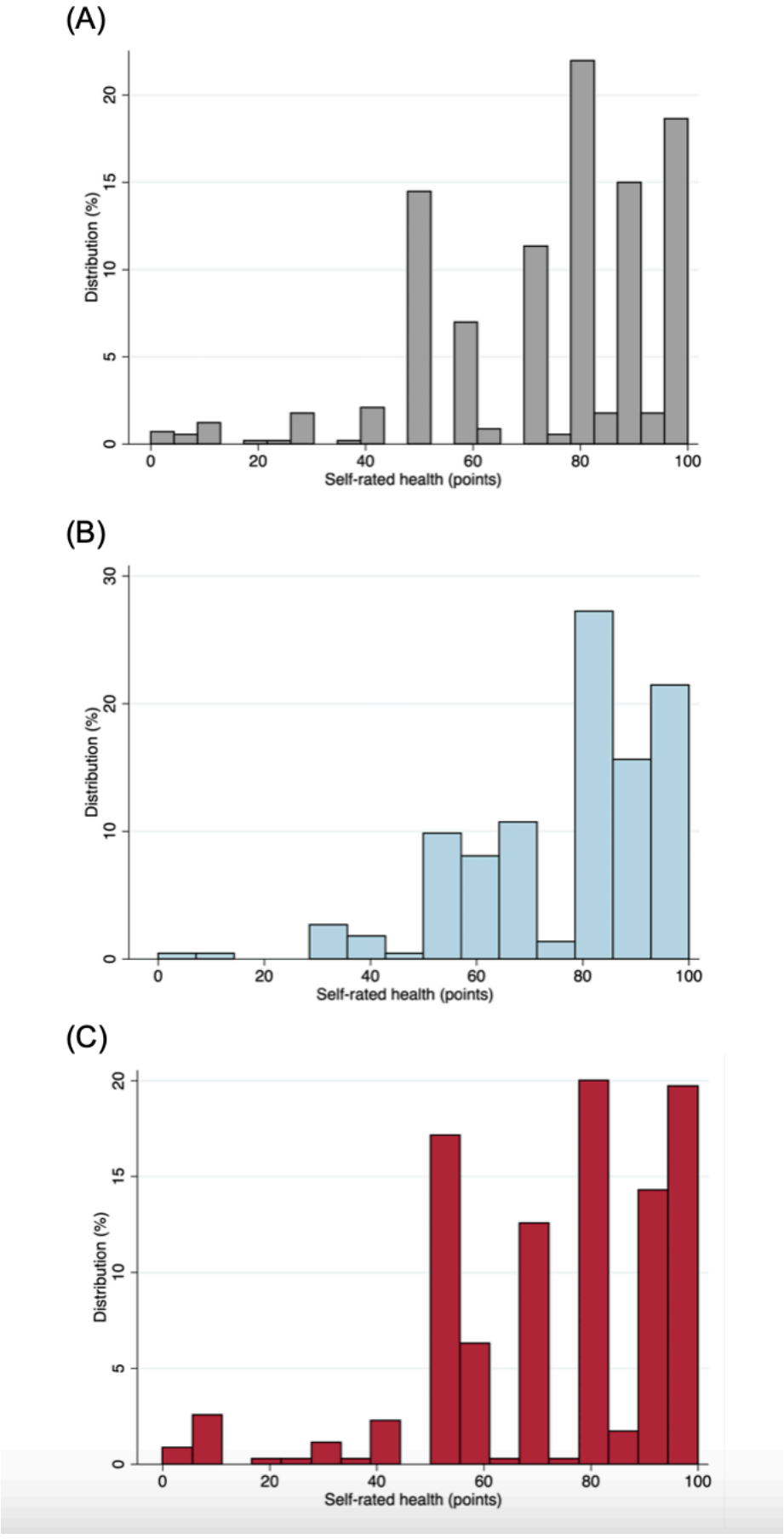
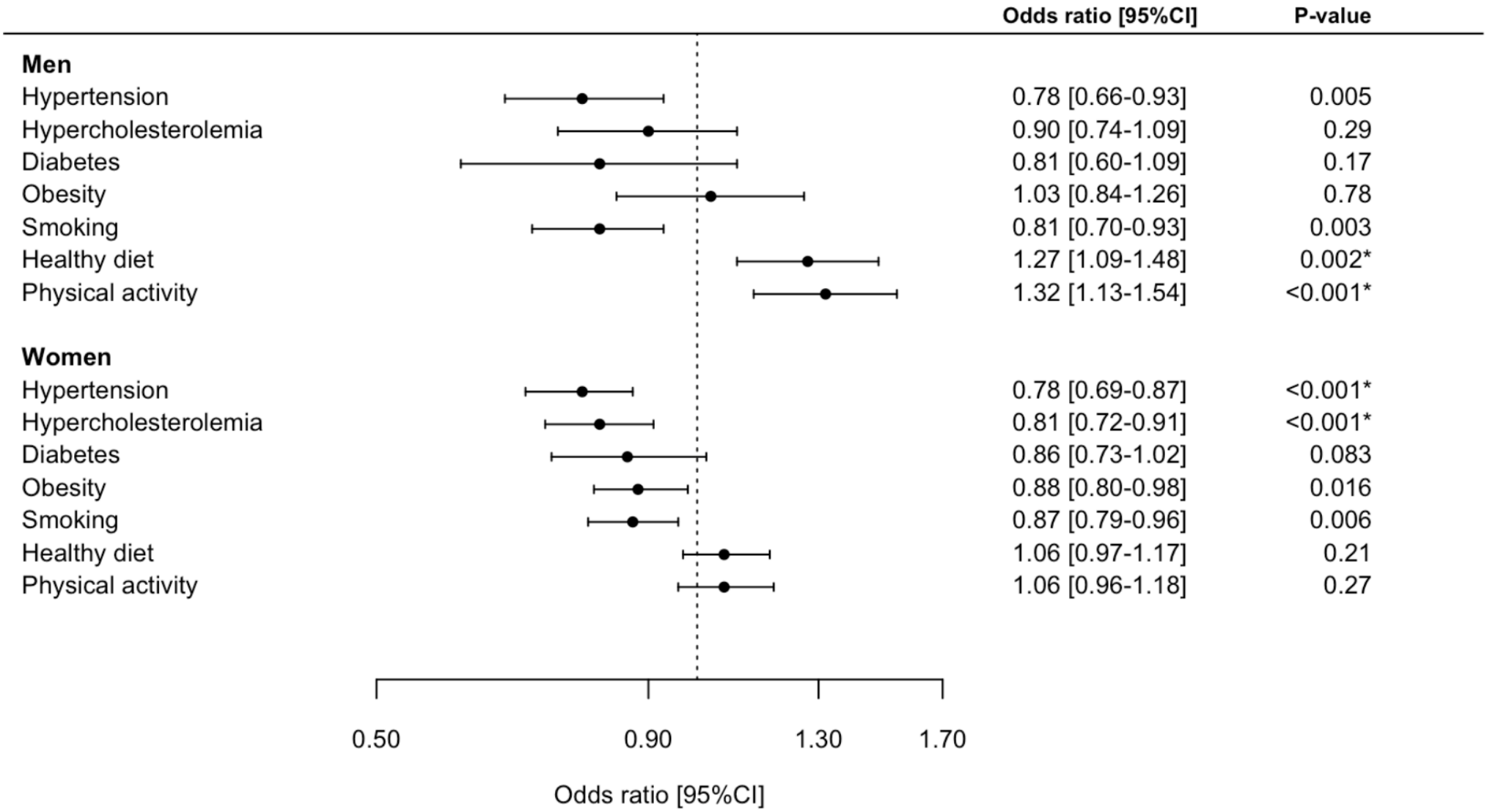

(A)
Distribution (%)
0
5
10
15
20
0
20
40
60
80
100
Self-rated health (points)
(B)
Distribution (%)
0
10
20
30
0
20
40
60
80
100
Self-rated health (points)
(C)
Distribution (%)
0
5
10
15
20
0
20
40
60
80
100
Self-rated health (points)

Figure 3.


Odds ratio [95%CI]
P-value
Men
Hypertension
0.78 [0.66-0.93]
0.005
Hypercholesterolemia
0.90 [0.74-1.09]
0.29
Diabetes
0.81 [0.60-1.09]
0.17
Obesity
1.03 [0.84-1.26]
0.78
Smoking
0.81 [0.70-0.93]
0.003
Healthy diet
1.27 [1.09-1.48]
0.002*
Physical activity
1.32 [1.13-1.54]
<0.001*
Women
Hypertension
0.78 [0.69-0.87]
<0.001*
Hypercholesterolemia
0.81 [0.72-0.91]
<0.001*
Diabetes
0.86 [0.73-1.02]
0.083
Obesity
0.88 [0.80-0.98]
0.016
Smoking
0.87 [0.79-0.96]
0.006
Healthy diet
1.06 [0.97-1.17]
0.21
Physical activity
1.06 [0.96-1.18]
0.27
0.50
0.90
1.30
1.70
Odds ratio [95%CI]

Supplemental Data

Is self-rated health associated with cardiovascular risk factors and disease in a low-income setting? A cross-sectional study from the Amazon Basin of Brazil

Anna E. Holm, MD; Laura Cordeiro Gomes; Alma Wegener, BSc; Karine O. Lima; Luan O. Matos; Isabelle V. M. Vieira; Molly D. Kaagaard; Manan Pareek, MD, PhD; Rodrigo Medeiros de Souza, PhD; Claudio Romero Farias Marinho, PhD; Tor Biering-Sørensen, MD, PhD, MPH; Odilson M. Silvestre, MD, PhD, MPH; Philip Brainin, MD, PhD

Content

Supplemental Methods: Echocardiography

End-diastolic dimensions of the left ventricle were obtained in the parasternal long axis view and measured at the level of the mitral valve leaflets. Left ventricular mass was accordingly calculated by the Devereux formula. End-diastolic and end-systolic volumes of the left ventricle were obtained in the apical two-chamber and four-chamber projections, allowing assessment of the left ventricular ejection fraction by the Simpson's biplane method. Left atrial volumes were measured by the area-length method in the same views and later divided by the body surface area to yield the left atrial volume index. In the apical four-chamber view we assessed mitral inflow velocities of early (E) and late (A) diastolic filling with pulsed wave Doppler and the deceleration time of the E-wave was measured. Pulsed wave color tissue Doppler imaging samples were placed above the septal and lateral mitral annulus to measure early diastolic velocity (e') of the left ventricle. In a focused right ventricular view, we assessed tricuspid regurgitation (TR) velocity by continuous wave doppler imaging.

Supplemental Table 1. Baseline clinical characteristics by sex

	Men n=224	Women n=350	P difference*
Baseline			
Age, years	40 ± 15	42 ± 15	0.28
Race, %			0.41
White	33 (15%)	44 (13%)	
Mixed	153 (68%)	262 (75%)	
Black	36 (16%)	40 (11%)	
Indigenous	1 (<1%)	3 (1%)	
BMI, kg/m^2	26 ± 4	28 ± 5	0.001
Abdominal circumference, cm	87 ± 13	88 ± 13	0.45
Asthma	4 (2%)	17 (4%)	0.06
COPD, %	2 (1%)	5 (1%)	0.57
History of MI, %	2 (1 %)	3 (1%)	0.96
Heart failure, %	3 (1%)	2 (1%)	0.33
Rheumatic heart disease, %	8 (4%)	10 (3%)	0.18
SBP, mmHg	133 ± 16	131 ± 22	0.18
DBP, mmHg	82 ± 12	82 ± 12	0.73
Risk factors			
Hypertension, %	37 (17%)	75 (21%)	0.15
Hypercholesterolemia, %	26 (12%)	63 (18%)	0.039
Diabetes, %	9 (4%)	24 (7%)	0.15
Obesity, %	31 (14%)	102 (29%)	0.001
Smoking, %	98 (44%)	119 (34%)	0.019
Healthy diet, %	99 (44%)	177 (51%)	0.14
Physical activity, %	107 (48%)	104 (30%)	0.001
Socioeconomic status			
Work status, %			0.001
Employed	70 (31%)	224 (64%)	
Self-employed	125 (56%)	103 (29%)	
Other	29 (13%)	23 (7%)	
Family income, BRL	1700 [1000, 2750]	1200 [800, 2000]	0.001
Rural living area, %	99 (44%)	126 (36%)	0.050
Biochemistry			
Blood sugar, mg/dL	100 ± 24	110 ± 67	0.047
Bilirubin, mg/dL	0.4 [0.3, 0.6]	0.3 [0.2, 0.4]	<0.001
Platelets, mm^3	220 ± 81	244 ± 62	0.001
Leukocytes, mm^3	6040 ± 1590	6632 ± 2002	0.001
Reticulocytes, %	0.75 ± 0.19	0.80 ± 0.22	0.44
Hemoglobin, g/dL	15 ± 1	13 ± 1	0.001
C-reactive protein, mg/L	0 [0, 0]	0 [0, 0]	0.59
Creatinine, mg/dL	1.0 ± 0.3	0.8 ± 0.2	<0.001
INR	1.03 ± 0.09	1.00 ± 0.11	0.001
Echocardiography			
LV ejection fraction<45%, %	11 (4.9%)	7 (2.0%)	0.05
LV hypertrophy, %	6 (2.7%)	11 (3.1%)	0.75
Diastolic dysfunction, %	3 (1.3%)	13 (3.7%)	0.09

COPD: chronic obstructive pulmonary disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, INR: international normalized ratio, LV: left ventricular

*P difference was calculated using the chi-square test, Student's *t*-test, and the Wilcoxon rank-sum test.
Normally distributed variables are displayed as mean ± standard deviation.
Non-normally distributed variables are presented as median [interquartile range].
Proportions are displayed as n (%).

Supplemental Table 2.

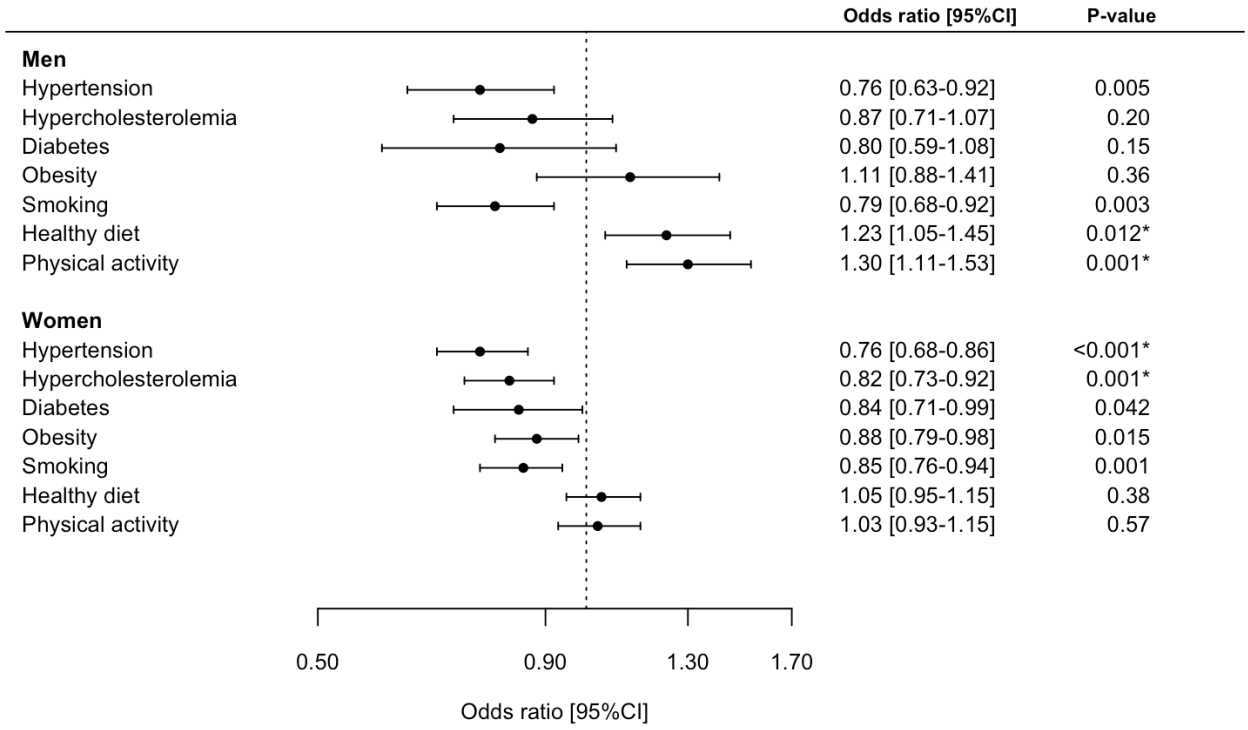
Association between self-rated health (per 10-point increase), cardiovascular risk factors and disease in the study population excluding recently treated malaria patients (n=504).

	Unadjusted odds ratio [95%CI]	P	Adjusted odds ratio [95%CI]*	P	P interaction sex
Risk factors					
Hypertension	0.76 [0.69 to 0.84]	<0.001	0.86 [0.77 to 0.96]	0.007	0.005
Hypercholesterolemia	0.83 [0.75 to 0.92]	<0.001	0.90 [0.80 to 1.00]	0.05	0.20
Diabetes	0.82 [0.71 to 0.95]	0.009	0.98 [0.83 to 1.17]	0.86	0.15
Obesity	0.91 [0.83 to 0.99]	0.036	0.96 [0.87 to 1.06]	0.40	0.36
Smoking	0.83 [0.76 to 0.91]	<0.001	0.93 [0.84 to 1.03]	0.16	0.003
Heathy diet	1.19 [1.00 to 1.18]	0.047	1.09 [1.00 to 1.19]	0.049	0.012
Physical activity	1.12 [1.03 to 1.22]	0.010	1.06 [0.96 to 1.17]	0.22	0.001
Subclinical cardiac disease					
LV ejection fraction <45%	0.92 [0.73 to 1.16]	0.49	1.02 [0.79 to 1.31]	0.88	0.91
LV hypertrophy	0.92 [0.74 to 1.15]	0.47	1.10 [0.84 to 1.44]	0.48	0.33
Diastolic dysfunction	0.85 [0.68 to 1.08]	0.18	1.05 [0.77 to 1.43]	0.77	0.23

*Multivariable models were mutually adjusted for cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity, smoking, healthy diet, physical activity) in addition to age, sex, work, family income, living area (rural/urban) and prior heart disease
LV: left ventricular

Supplemental Figure 1. Forest plot

Association between self-rated health (per 10-point increase) and cardiovascular risk factors stratified by sex. * indicates that the association remained significant in multivariable models.



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	5+9-10
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.