Nutrition 78 (2020) 110865

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Bioelectrical impedance analysis–derived phase angle is related to risk scores of a first cardiovascular event in adults

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ARTICLE INFO

Article History:

Keywords:
Phase angle
Risk scores
Cardiovascular event

ABSTRACT

Objective: The aim of this study was to investigate the association between phase angle (PhA) and first cardiovascular (CV) event risk.
Methods: This was a cross-sectional study. PhA was determined using a single-frequency bioelectrical impedance analyzer. Scores from the American College of Cardiology/American Heart Association (ACC/AHA; N = 455; 49% men) and the Framingham General Cardiovascular (FRS-CVD; N = 489; 49% men) were used to estimate the risk for a first CV event in adults. Logistic and multinomial regressions were used to evaluate the relationship between ACC/AHA and FRS-CVD risk scores (outcomes) and PhA. Additionally, the consumption of in natura or minimally processed foods was included in the models as an adjustment variable.
Results: Men and women, classified according to ACC/AHA ($P < 0.001$; $P = 0.035$) and FRS-CVD scores ($P = 0.002$; $P = 0.012$) as low risk for first event CV, presented higher PhA values than participants with elevated risk. However, only in men categorized as CV high risk, the third PhA tertile (>7.3°) was associated with a CV lower risk (ACC/AHA, odds ratio, 0.28; 95% confidence interval [CI], 0.14–0.56; FRS-CVD, relative risk ratio, 0.11; 95% CI, 0.03–0.37). The adjustment of all models for consumption of in natura or minimally processed foods did not change the results.
Conclusion: Higher PhA values were associated with lower risk for a first CV event in men classified in higher-risk categories. In natura or minimally processed food consumption did not influence the relationship between PhA and CV risk. These results may encourage future research about possible applications of PhA as an additional index in primary prevention of CV events.

Introduction

Chronic low-grade inflammation is critical in atherosclerosis pathogenesis and cardiovascular (CV) events and can lead to cellular injury [1]. The consumption of in natura or minimally processed foods, which compose a traditional diet, including fruits, vegetables, and cereals, can lead to cellular stability [2]. Phase angle (PhA), derived from bioelectrical impedance, relates to cellular health and is inversely associated with smoking status and inflammation [3,4], and positively with healthy food [2].

PhA is determined using bioelectrical impedance analysis (BIA), which is a safe and noninvasive method, usually applied to indirectly determine body composition [3]. PhA is a variable derived from resistance (R) and reactance (Xc) and is related to important cellular characteristics. Higher PhA values are suggestive of cellular health. In contrast, lower PhA values have been interpreted as indexes of cell loss and decreased cell membrane integrity [5,6].

PhA as a prognosis index of morbidity and mortality in several clinical conditions is related to decreases in this bioelectrical index caused by infection, malnutrition, disease-specific parameters, and inflammation [7]. Age, sex, body mass index (BMI), fat-free mass, and fluid distribution are major determinants of PhA in healthy individuals [8–11]. Studies of PhA in conditions not associated

This study was financed in part by the Coordenação de Aperfeiçoamento de Nível Superior – Brasil (CAPES) – Finance code 001 and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro - FAPERJ (grant no E-26/110.119/2013). All authors contributed to the conception or design of the study and contributed to the acquisition, analysis, or interpretation of data for the work. MRCP, JCK, DSC, and MFN drafted the manuscript. DSC, FFB, and EF critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy. The authors have no conflicts of interest to declare.

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https://doi.org/10.1016/j.nut.2020.110865
0899-9007/

with a serious decline in nutritional status or with specific clinical conditions are scarce, particularly in CV risk factors and CV events, except for heart failure [12,13].

Prevention of CV disease (CVD) demands timely identification of individuals at risk to target effective therapy in primary care [14]. CV risk prediction algorithms are important tools for identifying individuals who would benefit from pharmacologic interventions and lifestyle modification to manage risk factors, which contribute to reduction of CVD morbidity and mortality [15]. Among existing tools, sex-specific algorithms developed by the American College of Cardiology/American Heart Association (ACC/AHA) in 2013 and the general CVD risk function developed by Framingham investigators have been widely used to estimate risk for first CV event in 10 y [16,17].

PhA is related to cellular health and is inversely associated with inflammation and smoking status, which may lead to CV risk factors. However, the association between CV risk and PhA has not yet been thoroughly investigated. This relation may contribute to a possible applicability of this bioelectrical index in primary prevention of CVD. The main purpose of the present study was to investigate the association between PhA and first CV event risk scores.

Methods

Study design and participants

This cross-sectional study was nested within the Pró-Saúde cohort study, which is a prospective cohort study of non-faculty civil servants of a university located in the state of Rio de Janeiro, Brazil, focusing on the investigation of health-related social and behavioral determinants [18]. During the fourth phase of data collection (July 2012 and October 2013), additional assessments including bioelectrical impedance analysis (BIA) were performed, and a subgroup of 520 participants (250 men), 30 to 79 y of age with no previous CV events, were randomly selected to perform additional assessments including BIA. Blood samples and information on health status and behavioral characteristics were collected.

Three participants were excluded from the present analysis because of PhA values <4°, which were considered as extreme outliers. They could represent possible errors in measurement or register, and no conditions that could explain those values (e.g., advanced age, decline of nutritional status, and/or diseases) were found [5].

Additional exclusions were necessary due to specific characteristics of both CV risk prediction algorithms, such as previous history of CV events; age below or above the age range specified for risk score calculation by the ACC/AHA and Framingham General Cardiovascular (FRS-CVD); no information on race/skin color; previous diagnosis of hypertension and/or diabetes; treatment of hypertension; smoking status; no information on plasma total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels.

The ACC/AHA risk assessment equations provide sex- and race-specific estimates of the 10-y risk for CV events for men and women 40 to 79 y of age [16], and FRS-CVD predicts CV risk for adults between 30 and 74 y of age [17,19]. Due to the different cut point in the age, the number of individuals included in the risk assessment by the FRS-CVD was higher (N = 489) than in the ACC/AHA prediction model (N = 455).

This study was approved by the Ethics in Research Committee of the Institute of Social Medicine at the State University of Rio de Janeiro. All participants signed an informed consent form.

CV risk assessment: Prediction scores and risk factors

CV risk assessment was performed using scores developed by the ACC/AHA [16] and the FRS-CVD [17]. International scores were used to assess CV risk because there are no published data for the Brazilian general population.

The ACC/AHA pooled cohort risk equations estimate the 10-y risk for a first atherosclerotic CVD (ASCVD) event in non-Hispanic black and non-Hispanic white men and women from 40 to 79 y of age. Variables included in the prediction risk assessment model were sex; age; race; TC, HDL-C, and systolic blood pressure (SBP) values; treatment for high blood pressure; diabetes; and current smoking status. An excel spreadsheet enabled risk estimation: ≥ 7.5% was categorized as elevated 10-y risk for first ASCVD event and <7.5% as low risk [16].

FRS-CVD is referred to as a general CVD risk function. Risk factors used in its prediction model are similar to the ACC/AHA risk score, except for race, which is not considered. Risk categories used were 0 to <6% (low), 6% to 20% (intermediate), and >20% (high) in adults free of prevalent CVD, who were 30 to 74 y of age [16,17]. An excel spreadsheet recommended for risk calculation using lipids was used.

Some variables of both ACC/AHA [16] and the FRS-CVD [17] risk scores were obtained using a questionnaire applied by the Pró-Saúde cohort study. Researchers collected information on chronological age (participants ≥60 y of age were categorized as *older*) [20] and general health status. Participants were asked to inform previous diagnosis of hypertension and/or diabetes and if they have experienced a CV event (myocardial infarction, angina, or stroke) as well. In addition to the provided information about CV risk factors, long-term medication (hypoglycemic agents, insulin, and blood pressure medications) were considered as additional information for the diagnosis of hypertension and diabetes. Participants who informed a previous history of CV events did not apply for risk assessment in either score. Self-related information on participants' smoking status was obtained. Participants who never smoked were categorized as *never smokers*, those who quit smoking as *former smokers*, and those who responded positively were referred to as *current smokers*.

Blood samples were collected for determination of TC (mg/dL) and HDL-C (mg/dL). Cutoff values established for TC and HDL-C levels were 190 and 40 mg/dL, respectively [21].

Blood pressure was measured using a clinically validated oscillometric device (OMRON HEM-7113). Mean value of SBP was determined. Categories of SBP used were <120 mm Hg (normal) and ≥120 mm Hg (elevated) [22].

ACC/AHA CV risk score requires race to be classified into two categories: *blacks* and *white and others*. Information on race/skin color to estimate the CV risk with this prediction model for this study was obtained by self-classification according to categories adopted by the Brazilian Institute of Geography and Statistics census. To meet the score requirements, those self-declared as black were classified as *blacks*. Other racial classifications (white, mixed-race, Asians, and indigenous) were grouped as *white or others*.

Bioelectrical impedance analysis

BIA measurements were conducted using a BIA 450 Bioimpedance Analyzer (Biodynamics Corporation, Shoreline, WA, USA), which applies an alternating current of 800 μA at a single frequency of 50 kHz. Whole body bioelectrical analyses were carried out using standard protocol [23]. Whole body impedance consists of two components: R and Xc. R is the opposition to alternating electric current flow exerted by intracellular and extracellular ionic solutions. Xc is defined as a delay in the conduction of the applied current exerted by cell membranes and tissue interfaces. R and Xc were used to calculate PhA values by the following equation [24]:

$$\mathrm{PhA}(\circ) = \mathrm{arctangent}(\mathrm{Xc}/\mathrm{R}) \times (180\circ/\pi).$$

Food consumption evaluation

A food frequency questionnaire (FFQ) previously validated for the Brazilian population [25] was answered by all individuals. The FFQ listed 82 foods or food groups with predefined quantities presented in household measures or per unit of food. Participants were requested to inform the frequency and mean consumption for the previous 6 mo, and these values were transformed into daily frequency, converted into grams or milliliters and associated with the amount reported, to calculate the energy value of each food item [26].

Foods and culinary preparations mentioned in the FFQ were classified according to the NOVA classification, which considers the extent and the purpose of food processing into three groups:

- In natura or minimally processed foods and culinary preparations based on these minimally processed foods;
- Processed food; and
- Ultra-processed foods [27].

More details related to the FFQ and the classification of food items are presented in Berti et al. [28].

Considering the total energy intake and the energy of each NOVA food group, the energetic contribution of the three groups was calculted. In the present study, we focused on the energetic contribution of in natura or minimally processed foods owing to their role in promoting cellular stability.

Statistical Analysis

Statistical analyses stratified by sex were performed separately for each CV risk score prediction because sex variable is a PhA determinant [8–11]. Categorical variables were expressed as absolute and relative frequencies, and continuous variables, as means ± SD. Differences in age, lipid profile, SBP, and PhA values between men and women were tested using Student's *t* test. Differences in mean PhA values according to age, previous diagnosis of diabetes and hypertension, categories of SBP, TC, and HDL-C plasma levels, smoking status, skin color/race and to 10-y ASCVD event predicted with the ACC/AHA and FRS-CVD risk scores were

determined using Student's *t* test and one-way analysis of variance. Bonferroni post hoc test was used to perform pairwise comparisons of between-group means. Logistic regression models were fitted to evaluate the association of CV risk event (outcome) predicted by ACC/AHA and FRS-CVD risk categories with PhA tertiles (exposure). Additionally, the models were adjusted for the energetic contribution of in natura or minimally processed foods. Results were expressed as odds ratio (OR), relative risk ratios (RRRs), and 95% confidence intervals (CIs).

The inverse association between PhA and age observed in other studies justifies sorting the participants by age. The United Nations standard [23] establishes that people >60 y of age are categorized as older. According to this standard, the participants were classified in the age categories <60 and ≥60 y. Additionally, PhA values were grouped into tertiles with the following cutoff points: men: tertile 1 <6.6°, tertile 2 ≥6.6° to <7.3°, and tertile 3 ≥7.3°; women: tertile 1 <5.7°, tertile 2 ≥5.7° to 6.3°, and tertile 3 ≥6.3°; all participants: tertile 1 <6.1°, tertile 2 ≥6.1° to <6.8°, and tertile 3 ≥6.8°.

Significance level was set at 5%. Statistical analyses were conducted using SPSS version 17.0.1. (SPSS, Chicago, IL, USA) and Stata SE version 14.2 (StataCorp, College Station, TX, USA).

Results

According to each risk score model, >80% of participants were <60 y of age. Regarding previous diagnosis of diabetes or hypertension, a higher frequency of hypertension was observed in men (44%) and women (45%) included in the ACC/AHA prediction model. Hypertension was a highly frequent CV risk factor in both men (40%) and women (43%) in the FRS as well. More than 60% of all participants from both risk prediction models were categorized as never smokers. Regarding self-informed race/skin color, a variable included only in the ACC/AHA risk estimation, a higher frequency of white color was observed in men (51%) and women (42%). The ACC/AHA risk score predicted a high risk (≥7.5%) of a first CV event in 10 y in 40.5% of men and 16% of women. According to the FRS-CVD, most men were categorized as intermediate risk (60%), whereas almost 56% of women were categorized as low risk.

Considering men and women classified as low risk by the ACC/AHA and FRS-CVD scores, the energetic contribution of in natura or minimally processed foods and culinary preparations based on these foods was on average 59.4% (95% CI, 58.1−60.7) for men and 58.4% (95% CI, 56.8−60.1) for women; whereas those classified as elevated or high risk by the ACC/AHA and FRS-CVD scores consumed 61.7% (95% CI, 59.7−63.7) and 61.6 (95% CI, 58.9−64.3), respectively (Table 1).

According to risk scores, women showed significantly higher TC and HDL-C levels and lower SBP than men ($P < 0.001$). However, PhA was higher in men (6.9 ± 0.8°) than in women (6 ± 0.7°; $P < 0.001$; Table 2). PhA values were similar when the consumption of the in natura or minimally processed foods, processed foods, and ultra-processed foods ($P > 0.05$) was tested. However, PhA values were different, according to CV risk factors and to 10-y ASCVD event risk predicted by the ACC/AHA score for men and women. Men and women ≥60 y of age had lower mean PhA values than those <60 y ($P < 0.001$ and $P = 0.007$, respectively). No differences were found in PhA values according to categories of diagnosis for diabetes and hypertension, TC and HLD-C levels, SBP and race/skin color for either men or women. PhA values according to smoking status were only found in men, out of which current smokers had mean PhA value 0.6° lower than those who had never smoked ($P < 0.001$). Men and women in the low-risk category of first CV event according to ACC/AHA score had higher mean PhA values than those at elevated risk ($P < 0.001$). When only male and female never smokers and those <60 y of age were included in the analysis, differences in mean PhA values between CV risk categories ceased to exist ($P > 0.05$). When all smoking categories (even the never smokers), and participants <60 y of age were kept in the analysis, differences in mean PhA values between CV risk categories ceased to exist ($P > 0.05$). Men ($P < 0.001$) and women ($P = 0.035$) in the low-risk category of a first CV event according to

Table 1
Characteristics and 10-year ASCVD event predicted risk of male and female participants.

	ACC/AHA risk score		FRS risk score	
	Men n=222 n (%)	Women n=233 n (%)	Men n=238 n (%)	Women n=251 n (%)
Age, years				
< 60	183 (82.4)	187 (80.2)	199 (83.6)	204 (81.3)
≥ 60	39 (17.6)	46 (19.8)	39 (16.4)	47 (18.7)
Previous diagnosis, yes				
Diabetes [δ, a]	34 (15.3)	22 (9.4)	35 (14.7)	23 (9.3)
Hypertension [*,b]	88 (40.0)	104 (44.8)	93 (39.4)	107 (43.0)
Smoking Status				
Never smokers	138 (62.2)	142 (61.0)	152 (63.9)	158 (62.9)
Former smokers	54 (24.3)	69 (29.6)	56 (23.5)	70 (27.9)
Current smokers	36 (13.5)	22 (9.4)	30 (12.6)	23 (9.2)
Race/skin color (self-classification)				
Black	28 (12.6)	52 (22.3)	-	-
White	114 (51.4)	101 (43.3)	-	-
Mixed-race (*pardo*)	77 (34.7)	76 (32.6)	-	-
Other (indigenous and yellow)	3 (1.3)	2 (1.8)	-	-
Energetic contribution of *in natura* or minimally processed foods	(60.7)	(59.4)	(60.5)	(59.2)
10-year ASCVD event predicted risk	**ACC/AHA risk score**		**FRS-CVD risk score**	
	Low risk (< 7.5%)		Low risk (< 6%)	
	132 (59.5)	196 (84.1)	39 (16.4)	142 (55.6)
	Elevated risk (≥ 7.5%)		Intermediate risk (6-20%)	
	90 (40.5)	37 (15.9)	143 (60.1)	95 (37.8)
			High risk (> 20%)	
			56 (23.5)	14 (5.6)

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; MI, Myocardial infarction; ACC/AHA, American College of Cardiology/American Heart Association; FRS-CVD, Framingham General Cardiovascular Risk Prediction Model; CVD, Cardiovascular disease. Values are shown as N (total number of participants) and absolute (n) and relative frequencies (%). *Men: n=220, Women: n=232 (hypertension); **Men: n=219, Women: 230 (hypercholesterolemia); [δ]Women n=230 (diabetes) − ACC/AHA. [a] Women n=247 (diabetes)

[b]Men: n=236, Women: n=249 (hypertension)[c]Men: n=235, Women: 247 (hypercholesterolemia).

Table 2
Phase angle and continuous variables included in CV risk scores calculation and PhA values in male and female study participants.

	ACC/AHA		
	Men (n=222)	Women (n=233)	p-value
PhA,°	6.9 ± 0.8	6.0 ± 0.7	<0.001
Age, years	52.0 ± 7.3	52.5 ± 7.2	0.337
Total Cholesterol, mg/dl	200.5 ± 38.9	213.5 ± 41.1	0.001
HDL-c, mg/dl	46.4 ± 11.5	56.2 ± 12.0	<0.001
Mean SBP, mmHg	129.7 ± 17.1	124.4 ± 17.3	0.001
	FRS-CVD		
	Men (n=238)	Women (n=251)	p-value
PhA,°	6.9 ± 0.8	6.0 ± 0.7	<0.001
Age, years	51.0 ± 7.8	51.8 ± 7.9	0.296
Total Cholesterol, mg/dl	202.0 ± 39.0	213.1 ± 40.9	0.002
HDL-c, mg/dl	46.6 ± 11.6	56.1 ± 12.6	<0.001
Mean SBP, mmHg	129.5 ± 16.8	123.6 ± 17.2	<0.001

Abbreviations: CV, cardiovascular; PhA, phase angle; ACC/AHA, American College of Cardiology/American Heart Association; FRS-CVD, Framingham General Cardiovascular Risk Prediction Model; HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure. Values are shown as means ± SD. P-value determined by Student's *t*-test.

Table 3
Phase angle values according to cardiovascular risk factors and 10-year ASCVD event predicted by ACC/AHA score in male and female study participants.

	Men (n=222)		Women (n=233)	
	PhA°	*P*-value	PhA°	*P*-value
Age, years				
< 60	7.0 ± 0.8	< **0.001** [a]	6.1 ± 0.6	**0.007** [a]
≥ 60	6.4 ± 0.7		5.7 ± 0.8	
Diabetes				
Yes	6.7 ± 0.8	0.09 [a]	5.8 ± 0.8	0.188 [a]
No	7.0 ± 0.8		6.0 ± 0.7	
Hypertension				
Yes	7.0 ± 0.8	0.105 [a]	6.0 ± 0.7	0.294 [a]
No	6.8 ± 0.8		6.1 ± 0.7	
SBP, mmHg				
< 120	6.9 ± 0.7	0.634 [a]	6.1 ± 0.6	0.243 [a]
≥ 120	6.9 ± 0.8		6.0 ± 0.7	
TC, mg/dl				
< 190	6.8 ± 0.9	0.119 [a]	6.1± 0.8	0.209 [a]
≥ 190	7.0 ± 0.8		6.0 ± 0.6	
HDL-c, mg/dl				
> 40	7.0 ± 0.8	0.163 [a]	6.1 ± 0.9	0.641 [a]
≤ 40	6.8 ± 0.8		6.0 ± 0.7	
Smoking Status				
Never smokers	7.1 ± 0.8 *	<**0.001** [b]	6.1 ± 0.6	0.344 [b]
Former smokers	6.8 ± 0.8		6.0 ± 0.8	
Current smokers	6.5 ± 0.8 *		5.8 ± 0.6	
Race/skin color (self-classification)				
Black	7.0 ± 0.9	0.675 [b]	6. ± 0.6	0.468 [b]
White	6.9 ± 0.7		5.9 ± 0.7	
Mixed-race (*pardo*)	7.0 ± 0.8		6.0 ± 0.7	
Other (indigenous and yellow)	6.7 ± 0.9		6.1 ± 0.5	
10-year ASCVD event predicted risk (ACC/AHA)				
ACC/AHA (all participants)				
Low (< 7.5%)	7.1 ± 0.7	< **0.001** [a]	6.1 ± 0.7	**0.035** [a]
Elevated (≥ 7.5%)	6.6 ± 0.8		5.8 ± 0.7	
ACC/AHA (never smokers and participants < 60 years included) **				
Low (< 7.5%)	7.1 ± 0.7	0.835	6.2 ± 0.6	0.417
Elevated (≥ 7.5%)	7.1 ± 0.9		5.8 ± 0.3	
ACC/AHA (participants < 60 years and all smoking status included) ∞				
Low (< 7.5%)	7.1 ± 0.7	0.113	6.1 ± 0.6	0.643
Elevated (≥ 7.5%)	6.9 ± 0.9		6.0 ± 0.6	
ACC/AHA (participants < 60 and ≥ 60 years and never smokers included) δ				
Low (< 7.5%)	7.1 ± 0.7	0.303	6.1 ± 0.6	**0.045**
Elevated (≥ 7.5%)	6.9 ± 0.9		5.8 ± 0.6	

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; ACC/AHA, American College of Cardiology/American Heart Association; SBP, systolic blood pressure; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol. Values are shown as means ± SD. [a] P-value determined by Student's *t*-test
[b]P-value determined by ANOVA. *Bonferroni post hoc test: never smokers *vs* current smokers p= 0.001. ** Men: low risk = 104; high risk n=23. Women: low risk = 111; high risk n=2. ∞ Men: low risk = 132; high risk n=51. Women: low risk = 173; high risk n=14. δ Men: low risk = 104; high risk n=34. Women: low risk =124; high risk n=18.

the ACC/AHA score had higher mean PhA values than those at elevated risk. When participants of all ages and only those who never smoked were included, it was possible to observe that women in the low-risk category had a mean PhA value 0.3° higher than those categorized as high-risk ($P < 0.05$; Table 3).

Analyses in mean PhA differences according to CV risk factors and 10-y ASCVD event risk predicted by FRS are described in Table 4. Age and smoking categories were associated with differences in mean PhA values. Men and women <60 y had PhA values higher than participants >60 y: 7 ± 0.8° ($P < 0.001$) and 6.1 ± 0.6° ($P = 0.035$), respectively. Only male current smokers presented a mean PhA 0.6° lower than never smokers ($P < 0.001$). According to the FRS-CVD risk assessment score, a higher mean PhA value was observed in men at low risk when compared with those in the intermediate- and high-risk categories ($P < 0.002$). Higher mean PhA values were found in women categorized as low risk for a first CV event category when compared to the high-risk women ($P < 0.012$). Analyses with men and women included in the never smokers group and who were <60 y of age showed no differences in mean PhA values between FRS categories ($P < 0.05$). There were no differences in mean PhA values between CV risk categories when additional analyses with age and smoking status information were conducted among male and female participants ($P > 0.05$).

Considering the ACC/AHA score, PhA tertile 3 (≥7.3°) was associated with lower chance for a first CV event in men (OR, 0.28; 95% CI, 0.14–0.56). Analyses with all participants showed that tertile 2 PhA (≥6.1 to <6.8°) and tertile 3 PhA (≥6.8°) were associated with lower odds. Among women, PhA tertiles were not associated with odds of a first CV event estimated with ACC/AHA score (Table 5).

Associations between PhA and risk categories according to the FRS-CVD are shown in Table 6. In the intermediate-risk category, tertile 3 PhA (≥ 7.3°) was associated with 67% lower risk for a first CV event (RRR, 0.33; 95% CI, 0.11–0.97) in men. Second (≥ 6.6 to < 7.3°) and third PhA tertiles (≥ 7.3°) were associated with 76% (RRR, 0.24; 95% CI, 0.07–0.79) and 89% (RRR, 0.11; 95% CI, 0.03–0.37) lower risks for a first CV event in men categorized as being at high risk, respectively.

There was no association between PhA values and risk categories in FRS-CVD among women. Analysis of all participants showed that tertial 3 PhA (≥6.8°) was associated with a significant lower risk for CV event (RRR, 0.55; 95% CI, 0.34–0.91) in the intermediate-risk category. PhA values ≥6.1 to <6.8 and ≥6.8° were associated with 60% (RRR, 0.40; 95% CI, 0.21–0.78) and 79% (RRR, 0.21; 95% CI, 0.10–0.44) lower risk for a first ASCVD event in all participants in the high-risk category (Table 6).

The results of these associations do not change, even after adjustment for consumption of in natura or minimally processed foods and culinary preparations based on these foods (Tables 5 and 6).

Table 4
Phase angle values according to cardiovascular risk factors and 10-year ASCVD event predicted by FRS-CVD risk score in male and female study participants.

	Men (n=238)		Women (251)	
	PhA°	*P*-value	PhA°	*P*-value
Age, years				
< 60	7.0 ± 0.8	< **0.001** [a]	6.1 ± 0.6	0.005 [a]
≥ 60	6.4 ± 0.7		5.7 ± 0.8	
Diabetes				
Yes	6.7 ± 0.8	0.063 [a]	5.8 ± 0.8	0.146 [a]
No	7.0 ± 0.8		6.0 ± 0.7	
Hypertension				
Yes	7.0 ± 0.8	0.146 [a]	6.0 ± 0.7	0.249 [a]
No	6.9 ± 0.8		6.1 ± 0.7	
SBP, mmHg				
< 120	6.9 ± 0.6	0.671 [a]	6.1 ± 0.6	0.287 [a]
≥ 120	6.9 ± 0.8		6.0 ± 0.7	
TC, mg/dl				
< 190	6.8 ± 0.8	0.075 [a]	6.1± 0.8	0.235 [a]
≥ 190	7.0 ± 0.7		6.0 ± 0.6	
HDL-c, mg/dl				
> 40	7.0 ± 0.8	0.183 [a]	6.0 ± 0.7	0.330 [a]
≤ 40	6.8 ± 0.8		6.2 ± 0.9	
Smoking Status				
Never smokers	7.1 ± 0.8 *	< **0.001** [b]	6.1 ± 0.6	0.365 [b]
Former smokers	6.8 ± 0.7		6.0 ± 0.8	
Current smokers	6.5 ± 0.8 *		5.8 ± 0.6	
10-year ASCVD event predicted risk				
FRS-CVD (all participants) Low (< 6%)	7.2 ± 0.6 [#]	0.002 [b]	6.1 ± 0.7 [θ]	0.012 [b]
Intermediate (6-20%)	7.0 ± 0.8 [§]		5.9 ± 0.7	
High (> 20%)	6.6 ± 0.7 [# §]		5.7 ± 0.8 [θ]	
FRS-CVD (never smokers and participants < 60 years included) **				
Low (< 6%)	7.2 ± 0.6	0.827 [b]	6.1 ± 0.6	0.645 [b]
Intermediate (6-20%)	7.1 ± 0.9		6.2 ± 0.8	
High (> 20%)	7.0 ± 0.8		-	
FRS-CVD (participants < 60 years and all smoking status included) ∞				
Low (< 6%)	7.2 ± 0.6	0.08 [b]	6.1 ± 0.6	0.309 [b]
Intermediate (6-20%)	7.1 ± 0.8		6.0 ± 0.7	
High (> 20%)	6.8 ± 0.8		6.3 ± 0.4	
FRS-CVD (participants < 60 and ≥ 60 years and never smokers included) [δ]				
Low (< 6%)	7.2 ± 0.6	0.619 [b]	6.1 ± 0.6	0.122 [b]
Intermediate (6-20%)	7.1 ± 0.9		6.0 ± 0.7	
High (> 20%)	7.0 ± 0.6		5.6 ± 0.8	

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; FRS-CVD, Framingham General Cardiovascular Risk Prediction Model; SBP, systolic blood pressure; TC, total cholesterol; HDL-c, high density lipoprotein. Values are shown as means ± SD. [a] P-value determined by Student's *t*-test
[b]P-value determined by ANOVA. Bonferroni post hoc test: *never smokers *vs* current smokers p<0.001
[#]Low *vs* high p= 0.003
[§]Intermediate vs high p= 0.009. [θ] Low *vs* High p = 0.04. **Men: low risk n = 37; intermediate risk n= 92; high risk n=12. Women: low risk = 100; intermediate risk n=28. ∞ Men: low risk = 39; intermediate risk n= 129; high risk n=31. Women: low risk = 173;; intermediate risk n= 129; high risk n=14. [δ] Men: low risk = 37; intermediate risk n= 97; high risk n=18. Women: low risk =103; intermediate risk n= 48; high risk n=7.

Table 5
Association between PhA tertiles and ACC/AHA high risk score

ACC/AHA risk score		
Men (n=222)		
PhA tertiles	**Crude OR (95%CI)**	**Adjusted OR* (95%CI)**
<6.6° (n=70)	1.0 (reference)	1.0 (reference)
≥6.6°<7.3° (n=79)	0.54 (0.28, 1.03)	0.54 (0.28; 1.04)
≥7.3° (n=73)	0.28 (0.14, 0.56)	0.28 (0.14; 0.57)
Women (n=233)		
PhA tertiles	**Crude OR (95%CI)**	**Adjusted OR* (95%CI)**
<5.7° (n=68)	1.0 (reference)	1.0 (reference)
≥5.7°<6.3° (n=79)	0.57 (0.24, 1.35)	0.53 (0.22; 1.28)
≥6.3° (n=86)	0.52 (0.22, 1.22)	0.52 (0.22; 1.24)
All (n=455)		
PhA tertiles	**Crude OR (95%CI)**	**Adjusted OR* (95%CI)**
<6.1° (n=138)	1.0 (reference)	1.0 (reference)
≥6.1°<6.8° (n=158)	0.58 (0.36, 0.95)	0.56 (0.34; 0.91)
≥6.8° (n=159)	0.36 (0.21, 0.61)	0.36 (0.21; 0.61)

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association. Logistic regression model. Results presented as OR, odds ratio; CI, confidence interval.
*Models adjusted for the energetic contribution of in natura or minimally processed foods.

Discussion

The present study evaluated the association between PhA and CV risk assessment scores. FRS-CVD and ACC/AHA prediction models were used to estimate first CV risk; lower PhA values were found in men and women with high risk for CV events compared with those in low-risk categories. Furthermore, to our knowledge, this was the first study to point out that higher values of PhA may be associated with a lower risk for a first CV event in men, regardless of the consumption of in natura and minimally processed foods.

Among Brazilian individuals, an association between PhA and the consumption of foods such as extra virgin oil, cereals, legumes, and meat showed a weak positive correlation with PhA [29]. Moreover, high adherence to Mediterranean diet, which is considered a healthy dietary pattern, could improve cellular health in both sexes [2]. In the present study, the consumption of in natura or minimally processed foods did not influence the PhA values regardless of the CV risk obtained using the two risk scores applied, possibly due to the specificity of our group, in which about 56% (men) and 29% (women) presented high first event CV risk, unlike other studies, in which the participants were involved in changing lifestyle to prevent chronic diseases. Moreover, food consumption was similar among the different levels of risk.

Among CV risk factors included in both prediction models, only sex, age, and smoking status were related to PhA differences. Previous studies have shown that, in addition to BMI, sex and age were major predictors of PhA variations in healthy adults [8–11]. As expected, the present results showed men and women ≥60 y of age had lower PhA values compared with those <60 y. Additionally, men presented mean PhA values 0.9° higher than women. Similar to a previous study, we observed that male current smokers had lower mean PhA values compared with those who never smoked, even if other predictors were considered, whereas for female participants, there were no differences in PhA values regardless of smoking status [4].

PhA association with diabetes has been previously evaluated as well [30,31]. Lower PhA values were found in patients with type 2 diabetes compared with controls, and a longer disease duration was inversely correlated with PhA [30]. These results contradicted a previous study that found higher PhA values in older people with diabetes [31]. In the present study, neither positive nor negative previous diagnosis of diabetes resulted in PhA differences in men or women. Regarding race, a previous study showed black men and women had PhA values 0.276° and 0.315° higher than white men and women, respectively. Moreover, Asian women had PhA 0.38° lower than white women [10]. Ethnicity has been associated with PhA variations and have been considered as a variable that should be taken into account when determining PhA population reference values [32]. Present results showed no differences in PhA

Table 6
Association between PhA tertiles and FRS-CVD risk score

FRS-CVD risk score Men (n=238) PhA tertiles	Crude model Intermediate RRR (95%CI)	High RRR (95%CI)	Adjusted model* Intermediate RRR (95%CI)	High RRR (95%CI)
<6.6° (n=71)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥6.6°<7.3° (n=86)	0.43 (0.14, 1.29)	0.24 (0.07, 0.79)	0.42 (0,14; 1.25)	0.24 (0.07; 0.77)
≥7.3° (n=81)	0.33 (0.11, 0.97)	0.11 (0.03, 0.37)	0.33 (0.11; 0.97)	0.11 (0.03; 0.37)
Women (n=251) PhA tertiles	Crude model Intermediate RRR (95%CI)	High RRR (95%CI)	Adjusted model* Intermediate RRR (95%CI)	High RRR (95%CI)
<5.7° (n=74)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥5.7°<6.3° (n=84)	0.55 (0.28,1.07)	0.37 (0.10, 1.36)	0.53 (0.27; 1.04)	0.33 (0.09; 1.24)
≥6.3° (n=93)	0.53 (0.28,1.02)	0.24 (0.06, 1.00)	0.53 (0.28; 1.02)	0.25 (0.06; 1.03)
All (n=489) PhA tertiles	Crude model Intermediate RRR (95%CI)	High RRR (95%CI)	Adjusted model* Intermediate RRR (95%CI)	High RRR (95%CI)
<6.1° (n=145)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥6.1°<6.8° (n=170)	0.63 (0.38, 1.04)	0.40 (0.21, 0.78)	0.60 (0.36; 1.01)	0.37 (0.19; 0.73)
≥6.8° (n=174)	0.55 (0.34, 0.91)	0.21 (0.10, 0.44)	0.55 (0.33; 0.90)	0.21 (0.10; 0.43)

Abbreviations: FRS-CVD, Framingham General Cardiovascular Risk Prediction Model; CVD, Cardiovascular disease. Multinomial logistic regression. Results presented as RRR, relative risk ratio; CI, confidence interval.
*Models adjusted for the energetic contribution of *in natura* or minimally processed foods.

in either men or women when race/skin color was evaluated as a CV risk factor, which could be partially explained by the high level of miscegenation and ethnic diversity in Brazil [33].

The association between PhA and ASCVD risk was evaluated when multiple CV risk factors were considered simultaneously in CVD risk assessment prediction models. The ACC/AHA, but not the FRS-CVD, includes race, a social determinant of CV health [34], as a predictor of CV risk. Risk assessment by the algorithm proposed by Goff et al. [15] seemed relevant because of the great racial diversity of participants included in the Pró-Saúde Study. Additionally, regardless of a decline in CVD mortality between 2007 and 2013 among racial/ethnic groups in the United States, disparities continued to exist according to race and sex. Total mortality attributed to CVD was much higher among black women and men compared with whites and Hispanics of both sexes [35]. Stroke mortality rates and CVDs are higher among blacks than whites and other racial classifications in Brazil [36]. Present results showed that the high-risk category evaluated by the ACC/AHA score was associated with lower PhA values in men and women.

According to the present results, analyses with all participants showed that men in low- and intermediate-risk categories had higher PhA values than those classified as high risk. Similar to that observed among men, women in the low-risk category had significantly higher PhA values than those in the high-risk group. Regardless of methodological differences, these results were similar to those found in a previous study that showed an inverse association between CV risk assessed by FRS-CVD and PhA in older adults [37].

Additional analyses showed that differences in mean PhA values ceased to exist in both CV risk assessment scores with inclusion only of men and women <60 y of age and never smokers in analyses. Considering all risk factors included in both models, advanced age and current smoker status seem to be CV risk factors associated with lower PhA values. Among women, when participants < or >60 y of age and never smokers were included in the analysis, it was observed that those categorized such as low risk had higher PhA value. Therefore, older age appears to be a risk factor related to a lower mean of PhA in women evaluated by the ACC/AHA score.

Combination of multiple risk factors to estimate risk for developing CVD in both assessment models showed that cell stability and functionality, represented by PhA, were lower among individuals in the high-risk category for ASCV events. Atherosclerosis represents the most common pathologic cause of CVD, and a chronic low-grade inflammatory condition is now largely accepted as part of this process [38]. Risk factors, including hypertension, aging, diabetes, and smoking are associated with this chronic inflammatory reaction, which results in a vulnerable plaque prone to rupture, thrombosis and, ultimately, CVD events [1]. The relation between PhA and inflammation has been previously evaluated and C-reactive protein (CRP) levels were inversely associated with PhA and identified as its predictor in disease [6]. Recently, relation between PhA and inflammation was assessed and PhA exhibited a significant inverse association with interleukin-6, tumor necrosis factor-α, and CRP [39]. Therefore, it is possible to suggest that inflammation, due to a synergy between different CV risk factors, led to lower PhA values in individuals categorized as high risk.

Regression analysis results suggested that higher PhA values are indicative of higher cell membrane integrity and cellular health, which are independently associated with lower risk for first CV event estimated by both scores in men. In contrast, absence of association between PhA tertiles and CV event risk reduction in women may be explained by the low frequency of women in high-risk categories evaluated by the ACC/AHA (15.9%) and FRS-CVD (5.6%) scores. Lower CV risk estimated in women could be explained by lower frequencies of diabetes diagnosis and current smoking status, in addition to lower mean SBP and higher HDL-C levels, which are variables included in both risk prediction models.

Conclusion

The present study showed sex, age, and smoking status as CV risk factors associated with PhA values, and the consumption of the in natura or minimally processed foods did not influence the relationship between PhA and CV risk. However, when multiple CV risk factors were combined in two prediction models to assess risk for a first CV event, men and women with high CV risk had lower PhA values than those in low-risk categories. Furthermore, the association between higher PhA values with a lower risk for first CV event in men within high-risk categories evaluated by two

prediction models was an unprecedented finding. CV risk assessment scores are simple tools applied in routine clinical practice as well as BIA and PhA calculation. These results may encourage future research about a possible application of PhA as an additional index in CV primary prevention, particularly in men considered more prone to CV events, as CV risk assessment scores, BIA, and PhA calculation are simple tools applied in routine clinical practice. However, longitudinal studies would be required to confirm the protective effects of higher PhA values against the occurrence of a first CV event, mainly in men.

Acknowledgment

The authors acknowledge the participants of the Pró-Saúde Study, and the Interdisciplinary Nutrition Assessment Laboratory of the State University of Rio de Janeiro.

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