Prevalence of high risk for cardiovascular disease among the Brazilian adult population, according to different risk calculators: a comparative study

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Abstract *This study compares the proportion of the Brazilian adult population classified as being at high risk of cardiovascular disease (CVD) based on six different CVD risk calculators in order to assess the agreement across different tools. A cross-sectional study was conducted using laboratory data from the National Health Survey (NHS). The prevalence rates of high 10-year risk of CVD among individuals aged between 45 and 64 years were as follows: Brazilian Society of Cardiology (BSC) global risk score (GRS) – 38.1%; American College of Cardiology/American Heart Association (ACC/AHA) score – 44.1%; Framingham Heart Study/GRS – 19.4%; European Society of Cardiology SCORE – 14.6%; World Health Organization/International Society of Hypertension (WHO/ISH) score – 3.1%; and Lim et al. – 2.5%. The CVD calculators showed poor agreement for the identification of high-risk individuals and a high level of agreement for the identification of low/moderate risk individuals, except for the ACC/AHA risk score. The findings show that the proportion of individuals classified as eligible for preventive drug therapy varies from tool to tool, which could lead to the misinterpretation of risk, poor cost-effectiveness of therapy and difficulty implementing public policies.*

Key words *Cardiovascular diseases, Risk factors, Prevalence, Brazil*

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Introduction

Cardiovascular diseases (CVD) were responsible for approximately 18 million deaths in 2016, with around 80% of CVD deaths occurring in middle and low-income countries[1]. These diseases are associated with poor socioeconomic conditions (such as poverty and low income and education levels[2,3]), rapid urbanization, increased life expectancy[1-3], behavioral risk factors (smoking, drinking, poor diet, sedentarism) and metabolic risk factors (obesity, high blood sugar, high blood pressure, hyperlipidemia)[1-4]. It is known that combined overlapping risk factors (RFs) result in an increased risk of CVD. The early detection of individuals at high risk of CVD and timely treatment is therefore a priority[1,4].

The World Health Organization (WHO) recommends a number of population-wide policy interventions to encourage the primary prevention of CVD, including regulatory measures such as taxing tobacco, alcohol and ultra-processed foods[5,6] and the creation of environments that facilitate healthy lifestyles and empower individuals and communities to make healthy choices[6]. Also within the context of primary prevention – defined in this case as prevention prior to a cardiovascular event – the WHO recommends the identification of high-risk individuals using risk scores or calculators to estimate the combined risk of CVD[4].

The identification of high-risk individuals permits the adoption of specific preventive measures (counseling and drug therapy), including the prescription of statins[4] or drug therapy in the prehypertension stage[7,8]. Both these interventions are aimed at preventing death and non-fatal adverse cardiovascular events, particularly coronary artery disease (CAD) and strokes, the two leading causes of death in Brazil[1,9]. CVD risk calculators have therefore become important tools for supporting public health actions, particularly in primary health care services, and informing decision-making about counseling and treatment[4]. However, selecting which calculator to use in Brazil remains a topic of debate, as an equation derived from national cohort studies representing the country's specific population characteristics (racial composition, socioeconomic and geographic conditions, specific laboratory reference values, etc.) does not yet exist, meaning that risk estimations can often be inaccurate.

Current CVD risk calculators differ according to the characteristics of the population from which they were derived (sex, age group, race, etc.)

and the presence or absence of population-specific risk prevention measures, which vary over time and depending on local health policies[10]. Although calculators tend to include similar RFs, the CVD risk weightings assigned to individual factors and the 10-year CVD outcomes and how they are adjudicated can vary from tool to tool[10]. For example, some calculators only estimate the risk of CVD death, while others include various non-fatal cardiovascular events. In addition, each calculator adopts its own threshold for high risk of CVD, taking into account the above characteristics and the risk authors consider acceptable for the indication of statins based on the medicine's country-specific benefit-risk ratio[11].

The objective of this study was therefore to compare the proportion of the Brazilian population at high risk of CVD estimated using different risk calculators in order to assess the agreement across different tools. The implications of the findings for preventive interventions in high-risk individuals and policy planning in Brazil are then discussed.

Methods

We conducted a cross-sectional study using data from the National Health Survey (NHS), a nationwide study undertaken by the Brazilian Institute of Geography and Statistics (IBGE, acronym in Portuguese) and Ministry of Health in 2013 and completed with a laboratory subsample in 2014 and 2015[12].

We used a subsample consisting of 25% of the census tracts selected for the 2013 NHS using the same stratified sampling design as the survey, applying probability inversely proportional to the difficulty of data collection[11]. The following three-stage cluster sampling design was used: Stage 1 – selection of primary sampling units (census tracts or composition of tracts); Stage 2 – random selection of a fixed number (10 to 14) of permanent private households from each census tract; Stage 3 – random selection of one person aged 18 years and over living in each household from a list of eligible participants drawn up at the time of the interview[11]. Based on the percentage of the NHS census tracts used to undertake the laboratory tests and a non-response rate of 20%, the expected number of individuals with laboratory data was approximately 12,000[11]. Biochemical tests were performed on 8,952 individuals in Brazil as a whole. Further details about the selection process[12,13], aspects related to specimen

collection[12,13], blood pressure measurement[16], assessment of smoking and prior CVD[17,18], and thresholds for estimating the proportion of the population with diabetes[13] and above-normal cholesterol levels[14,15] can be found in previous studies.

Individuals were classified as being at high or low/moderate risk of CVD (hereafter called low risk) using the following six calculators/scores: 1) The calculator recommended by the Brazilian Society of Cardiology (BSC), based on the Framingham Heart Study-derived calculator plus other criteria detailed below; 2) The pooled cohort equation, which was introduced by the American College of Cardiology and American Heart Association (ACC/AHA) in 2013[20] and uses data from various cohort studies in the United States to derive and validate new sex and age-specific equations; 3) The global risk score derived from the 2008 Framingham Heart Study (GRS-FHS)[21]; 4) The SCORE calculator, proposed by the European Society of Cardiology. Derived from various European cohort studies, SCORE proposes two estimation equations for coronary heart disease and non-coronary cardiovascular disease calculated for high-risk (Eastern) and low-risk (Western) regions of Europe. For the purposes of the present study, we cautiously chose the equation for high-risk regions, because we did not know the risk of the Brazilian population[22]; 5) Country-specific risk charts developed by Lim et al.[23] using simulation models[23]; 6) The calculator proposed by the WHO/International Society of Hypertension (WHO/ISH) for 14 WHO epidemiological sub-regions. For the purposes of this study, we selected the Americas sub-region B, which includes Brazil[24] (Table 1). These calculators were chosen because they are the most commonly used tools in clinical practice or are specific to the region in which Brazil is located.

It is important to note that age groups, variables, CVD outcomes, and thresholds for high-risk of CVD differ from calculator to calculator, as shown in Table 1.

With regard to the calculator recommended by the BSC[19], individuals are classified based on an global risk score (GRS)[21] (high-risk threshold of > 20% for men and > 10% for women) or the presence of other variables: individuals with chronic kidney disease (glomerular filtration rate of <60ml/min and not on dialysis); individuals with LDL cholesterol of ≥ 190mg/dL; individuals with LDL cholesterol of ≥ 70 to < 190mg/dL, together with at least one other risk factor (men aged ≥ 48 years and women aged ≥ 54 years, time

since diagnosis of diabetes ≥ 10 years, smoker, high blood pressure – systolic or diastolic pressure ≥ 140 and ≥ 90mmHg, respectively); and individuals with metabolic syndrome based on International Diabetes Federation criteria[28] (triglycerides were replaced by total cholesterol due to the lack data on the former)[12,14]. The BSC definition of high risk of CVD also includes individuals with subclinical atherosclerosis, abdominal aortic aneurysm, a family history (first degree relative) of early-onset CVD, and albuminuria[19]. These problems were not included in the analysis due to lack of information on the conditions in the PNS database.

With regard to statistical analysis, participants with known CVD were excluded from the analysis because the calculators used in this study also exclude these cases. To permit comparisons across the different tools, an additional analysis was performed of participants aged between 45 and 65 years, the age group covered by all the calculators (n = 2,791). The risk estimation tools with continuous results (SCORE, ACC/AHA) or scores (GRS) were analyzed using a binary classification, where individuals above and below the threshold were assigned a value of 1 for high risk or 0 for low risk, respectively. The tools developed by Lim et al.[23], the WHO/ISH[24] and BSC[19] calculate risks dichotomously. Agreement across the calculators was assessed by comparing the CVD risk classifications (prevalence of high and low risk) using the percent of pairwise agreement and the BSC calculator[19] as a reference. The BSC calculator was used as a reference because it is the tool recommended by national guidelines. The percent agreement measures the proportion of individuals at high or low risk of CVD based on the calculator in question and on the BSC calculator.

The NHS was approved by the National Research Ethics Committee[17].

Results

Figure 1 shows the prevalence of high 10-year risk of CVD for the population aged between 45 and 64 years using the threshold suggested by each calculator. The calculator that showed the highest prevalence rate was the ACC/AHA risk score (44.1%; 95%CI, 41.7-46,5), followed by BSC (38.1%; 95%CI, 35.8-40.4), GRS (19.4%; 95%CI, 17.5-21.4), SCORE (14.6%; 95%CI, 12.9-16.4), WHO/ISH[24] (3.1%; 95%CI, 2.4-4), and Lim et al.[23] (2.5%; 95%CI, 1.8-3.3).

Table 1. Characteristics of the cardiovascular disease risk calculators assessed by the study –age group, variables used, 10-year CVD outcomes and high-risk thresholds.

CVD risk calculator	Age group	Variables used	10-year outcomes	Threshold
ACC/AHA[20]	40–79	Age, sex, SBP, use of antihypertensive drugs, TC, HDL-c, DM, smoking	Fatal coronary disease, non-fatal AMI and stroke	≥ 7.5%
Framingham (ERG)[21]	30-74	Age, sex, SBP, use of antihypertensive drugs, TC, HDL-c, DM, smoking	Fatal and non-fatal cardiovascular disease (coronary, cerebrovascular, heart failure, intermittent claudication)	≥ 20%
GRS – recommended by the BSC[19]	30-74	Same as the GRS or subclinical atherosclerosis * or abdominal aortic aneurysm or colesterol LDL-c ≥ 190 mg/dL or chronic kidney diseases or diabetes with LDL 70-190mg/dL and RS**; SCA ***	Fatal and non-fatal cardiovascular disease (coronary, cerebrovascular, heart failure, intermittent claudication)	≥ 10% women ≥ 20% men; plus other criteria
WHO/ISH[24]	40-79	Age, sex, SBP, TC, DM, smoking	Fatal or non-fatal AMI or stroke	≥ 20%
Lim et al.[23]	40-79	Age, sex, SBP, BMI, smoking	Coronary disease or stroke (fatal)	≥ 15%
SCORE (High-Risk –TC)[22]	45-64	Age, sex, SBP, TC, smoking	Cardiovascular death (coronary, stroke, arrhythmia, aortic aneurysm or peripheral vascular disease)	≥ 5%

TC: total colesterol, DM: diabetes mellitus, HDL-c: high-density lipoprotein, AMI: acute myocardial infarction, SBP: systolic blood pressure.

ACC/AHA- American College of Cardiology/American Heart Association[20] WHO/ISH – World Health Organization/International Society of Hypertension[24]; Global risk score (GRS) recommended by the Brazilian Society of Cardiology (BSC)[19] – Framingham Heart Study (GRS)[21], European Society of Cardiology SCORE[22].

*Although atherosclerosis is part of the score recommended by the BSC, subclinical atherosclerosis was not included due to lack of data. **Stratified by risk: Age ≥ 48 years for men and ≥ 54 for women; time since diagnosis of diabetes > 10 years; family history (first degree relative) of early-onset CVD (< 55 years for men and < 65 for women); smoking (at least one cigarette in the last month); systemic hypertension; metabolic syndrome (MS), based on the International Diabetes Federation criteria; albuminuria > 30 mg/g of creatinine and/or retinopathy; glomerular filtration rate < 60 mL/min. *** SCA: Subclinical atherosclerosis: Ultrasonography with presence of carotid plaque > 1.5 mm; ABI < 0.9; coronary calcium score > 10 Agatston score; presence of atherosclerotic plaques on coronary angiogram; LDL-c between 70 and 189 mg/dL, with global risk score of > 20% in men and > 10% in women.

Figure 2 shows the prevalence of high risk of CVD using the same thresholds, but this time with the different age groups covered by each measure. The calculator that showed the highest prevalence rate was once again the ACC/AHA risk score (40-79 years – 39.4%; 95%CI, 37.6-41.3), followed by BSC (30-74 years – 28.8%; 95%CI, 27.4-30.2), GRS (30-74 years – 14.7%; 95%CI 13.6-15.9) and SCORE (45-64 years – 14.6%, 95%CI 12.9-16.4); with Lim et al. and WHO/ISH once again showing the lowest prevalence rates.

Table 2 shows the prevalence of high risk of CVD together with the percent agreement between each tool and the BSC calculator. The calculator that showed the highest level of agreement with the BSC calculator for prevalence of high-risk of CVD was GRS (50.9%; 95%CI, 47.1-54.7), which is to be expected given that GRS is part of the BSC calculator's estimation equation. The findings also show that 43.5% (95%CI, 39.7-47.3) of the high-risk individuals predicted by the BSC calculator were considered high-risk by
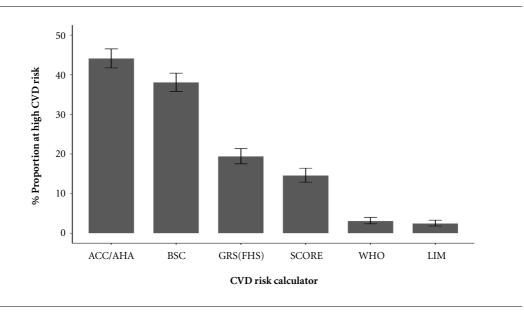
Figure 1. Proportion of the population aged between 45 and 64 years at high-risk of cardiovascular disease (CVD) based on the different CVD risk calculators, Brazil. National Health Survey - 2013, 2014-2015.

the ACC/AHA risk score, compared to 29.4% (95%CI 26-33.1) for SCORE and less than 10% for WHO[24] and Lim et al.[23].

With regard to percent agreement for the prevalence of low risk, the calculator that showed the lowest level of agreement was the ACC/AHA risk score. The findings show that 55.5% the low-risk individuals predicted by the BSC calculator were considered low-risk by the ACC/AHA risk score. GRS showed 100% agreement with the BSC calculator, which is to be expected considering that the latter uses the GRS, albeit with lower thresholds and including other categories in the definition of high-risk. The percent agreement between SCORE and the BSC calculator was 94.6% (95%CI, 92.8-95.9), while the level of agreement between WHO and Lim et al.[23] and the BSC calculator was over 99%.

Discussion

In general, the CVD risk calculators assessed by this study showed a low level of agreement with the BSC calculator for detecting high risk of CVD and a high level of agreement for identifying individuals at low risk of CVD, except the ACC/AHA risk score. The findings also show that the proportion of individuals classified as being at

high risk of CVD by these commonly used calculators varied considerably, reaching up to 39% of the population aged between 45 and 65 years. This means that the proportion of individuals eligible for preventive drug therapy varies from tool to tool, which could lead to the misinterpretation of risk, poor cost-effectiveness of therapy and difficulty implementing public policies.

The low level of agreement for the identification of high-risk individuals found by the present study has been reported by previous studies. Using data from hypothetical patients and 24 calculators, Allan et al.[26] found poor agreement between pairs of tools (67%), highlighting the need to calibrate calculators to specific populations to ensure the effective implementation of clinical guidelines on preventive drug therapy[24]. Risk scores have been developed or calibrated mainly for populations in the United States and Europe, with a lack of studies in low and middle-income countries, where socioeconomic factors such as access to health care and racial and cultural characteristics have a particularly strong impact on risk of CVD[10].

Other studies draw attention to the overestimation of risk, especially by the ACC/AHA risk score. In a prospective study with 4,000 male patients in the United States, DeFilippis et al.[26] found that discordance between events predict-
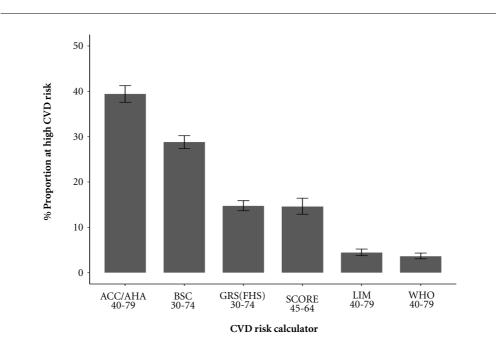
Figure 2. Proportion of the population at high-risk of cardiovascular disease (CVD) by the age groups and thresholds adopted by the different CVD risk calculators, Brazil. National Health Survey - 2013, 2014-2015.

Table 2. Percent agreement across the six CVD risk calculators for the classification of individuals as high or low-risk using the calculator recommended by the Brazilian Cardiology Society as a reference, Brazil. National Health Survey 2014-2015.

CVD risk calculator	Prevalence % (CI 95%)	Agreement for high-risk (%)	Agreement for low-risk (%)
BSC	38.1(35.8;40.4)	reference	reference
ACC/AHA	44.1(41.7;46.5)	43.5(39.7;47.3)	55.5(52.4;58.6)
GRS (FHS)	19.4(17.5;21.4)	50.9(47.1;54.7)	100(100;100)
WHO	3.1(2.4;4)	7.6(5.8;9.9)	99.7(99.3;99.8)
LIM	2.5(1.8;3.3)	5.8(4.2;7.9)	99.6(99.2;99.8)
SCORE	14.6(12.9;16.4)	29.4(26;33.1)	94.6(92.8;95.9)

Source: National Health Survey - 2013, 2014-2015.

ed using the Framingham Risk Score[21] and ACC/AHA risk score[20] and observed events ranged from 37 to 154%. The authors suggest that these differences may be due mainly to: the use of old cohorts to derive the risk scores – with probable changes in population characteristics over time, improvements in therapy and the identification of new risk factors in recent years; difficulties in assessing certain risk factors, such as the number of cigarettes smoked and alcohol intake; or study limitations affecting the identification of events. In a study using a 1997-2001 to 2012 cohort of patients aged 55 years and older without previous CVD living in Rotterdam, Kavousi et al.[27] observed an overestimation of risk, drawing attention to the fact that almost all men and 65%

of women would be eligible for statins based on the ACC/AHA risk score.

Within the Latin American context, the findings of a study conducted in Honduras[28], a lower middle-income country, which calculated the risk of CVD using four different calculators showed that an elevated proportion of individuals were high-risk. The prevalence of high-risk men and women based on the ACC/AHA risk score, GRS and MESA Risk Score was 62.0% and 29.8%, 46.1% and 15%, and 70.6% and 17.7%, respectively[28]. The findings of a study[10] undertaken with 2,183 individuals from different regions of Peru assessing agreement between seven CVD risk scores were similar to ours. Agreement between the scores was poor and the variation in proportion of high-risk individuals was high: 29% (16.9-31.0%) based on the ACC/AHA risk score to 0.6% (0.2-8.6%) using the WHO score. The authors of this study[10] concluded that there is uncertainty as to the selection of an appropriate CVD risk calculator in Peru and other low and middle-income countries, which is corroborated by the findings of the present study.

As mentioned above, the low level of agreement across scores for the identification of high-risk individuals may be related to the different CVD outcomes included in each score and the underlying risk factors assigned to different populations. In this respect, data supporting these factors is more readily available in developed countries due to the larger number and frequency of longitudinal studies. Other factors may include changes in RFs and the behavior of the population towards these factors over time, highlighting the need for prevalence and follow-up studies using biochemical and anthropometric data to measure trends[10].

A meta-analysis highlighted the benefits of statins for primary prevention, showing that they reduce the risk of mortality from major cardiovascular events[9]. These findings, combined with drug safety profiles and the reduced cost of these medicines has resulted in more permissive criteria for the indication of statins in some countries[9]. However, there are still divergences regarding the definition of the threshold for high risk of CVD in each score. This definition considers the risk-benefit of statins[9]. Traditionally, the high-risk threshold for the GRS has been set at >20%. A new score proposed by the ACC/AHA in 2013[28] considers only fatal and non-fatal acute myocardial infarctions and strokes and reduces the risk threshold to >7.5%[28], thus increasing the proportion of the population classified as being at high

risk of CVD. Some authors have criticized the reduction of the threshold, claiming that it results in overmedicalization and additional costs for certain countries, particularly those with limited resources[29]. A cost-effectiveness analysis conducted in Brazil[30] suggests that the use of moderate-dose statins is cost-effective for high-risk patients, considering the GRS and threshold of > 20%. However, it is not known whether the same is true for more permissive thresholds. In addition, consideration should be given to the availability of financial resources for the large-scale expansion of therapy.

Regardless of which calculator is used to calculate the risk of CVD, it is important to emphasize that CVD scores have limitations, in so far as they generally assess 10-year risk – meaning they may underestimate lifetime risk[28] – and do not include proximal risk factors such as socioeconomic conditions[31] – which are related to access to quality health care – and geographic location. Moreover, they do not consider modifying factors that increase the risk of CVD – which should be analyzed individually – such as family history of early-onset CVD[31], familial hypercholesterolemia[32], chronic kidney disease, inflammatory diseases, and smoking[33]. Thus, for the proper application of these tools in clinical practice, it is important to carefully assess the real CVD risk and individualize treatment. Moreover, although the increase in risk of CVD due to RFs such as diabetes and high blood pressure may be gradual and can be reduced with treatment, some scores assess this risk dichotomously, while others do not include the treatment of these conditions as variables in the risk prediction model[33].

In the absence of a specific risk calculator for the Brazilian population, we will have to use one of the risk prediction tools cited above to calculate risk of CVD and assess eligibility for primary prevention, as recommended by the WHO[4]. However, when selecting the risk calculator it is important to be fully aware of the differences between the tools in terms of risk factors and CVD outcomes and choose the appropriate high-risk threshold. In addition, it is important to bear in mind that agreement across tools for the identification of high-risk individuals is poor, while the level of agreement for the assessment of low risk is high – except for the AHA/ACC score, which adopts more permissive criteria for the use of statins by reducing the high-risk threshold to >7.5%[21]. In other words, with the majority of calculators, individuals identified as low-risk are very likely to be at low-risk; however, in the case

of individuals identified as being at high risk, careful assessment is necessary before introducing drug therapy.

This study has some limitations. First, not all the equations used by the calculators were available and graph-based scores do not provide continuous risk assessments. Second, comparability may have been affected by differences in the definitions of predictors and CVD outcomes used in the scores assessed by this study, as shown in Table 1. However, the aim of this study was to compare the calculators precisely as they are, as recommended in the Brazilian guidelines – i.e. the tools applied in everyday clinical practice – in order to show just how important it is to understand the definitions used in the scores and each risk assessment tool's limitations. Moreover, we believe that most health professionals that apply the scores in clinical practice are not necessarily aware of the technical details and modelling behind the "high 10-year risk of CVD" label, potentially resulting in the introduction of ineffective drug therapy for the prevention of CVD.

While doubts about the identification of individuals who should receive drug therapy to prevent CVD prevail in everyday clinical practice, non-pharmacological interventions – which encourage the adoption of healthy lifestyle habits such as stopping smoking, healthy eating, regular physical exercise and reducing alcohol intake – and population-wide interventions, regardless of individual baseline risk, should be implemented on a large scale to reduce CVD morbidity and mortality[34]. With regard to specific preventive measures directed at high-risk populations, there is an urgent need to develop a Brazilian CVD risk calculator derived from data from national cohort studies or validate international calculators that correctly identify high-risk individuals to ensure effective treatment and inform policy planning. It is also important to advance efforts to define reference values for laboratory tests in Brazil based on nationwide studies taking into account ethnic diversity and local social and cultural characteristics, establishing recommended ranges as proposed by the NHS laboratory[35].

Conclusion

This study analyzed the proportion of individuals from a representative subsample of Brazil's National Health Survey classified as being at high-risk of CVD based on six different risk scores. Using the score recommended by the Brazilian Society of Cardiology as a reference, in general, the other CVD risk calculators assessed by this study showed low sensitivity and high specificity for the identification of high-risk individuals. In addition, these scores, currently the most commonly used CVD risk assessment tools, showed a wide variation in the proportion of individuals classified as being at high risk of CVD. In the absence of a specific risk calculator derived from national cohort studies or validated for use with the Brazilian population, the generalization of risk equations and definition of thresholds for drug therapy should be rediscussed for each context considering the cost-effectiveness of the recommendations.

Collaborations

DC Malta participated in study conception, planning and design, data interpretation and in drafting the article and revising it critically for important intellectual content. PC Pinheiro participated in study planning, statistical analysis, writing the results section and revising the article critically for important intellectual content. FM Santos and LCC Brant participated in data interpretation and in drafting the article and revising it critically for important intellectual content. ALP Ribeiro participated in data interpretation and in revising the article critically for important intellectual content.

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