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# Relationship between genetic ancestry and metabolic syndrome in community-dwelling old adults

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# ABSTRACT

Genetic ancestry may contribute to ethnic differences in the risk of metabolic disorders. Aging leads to a worse ability for homeostasis maintenance, favoring the establishment of metabolic disorders.

*Purpose*: This study aimed to evaluate the relationship between the degree of genetic ancestry (European, African, and Amerindian) with the Metabolic Syndrome (MetS) diagnosis and its diagnostic components separately, in community-dwelling old adults. One hundred and sixty-one community-dwelling old adults volunteered in this study. Sociodemographic data and health history were recorded. Venous blood samples were withdrawal for biochemical analysis and DNA extraction aiming to obtain genetic ancestry estimates (Amerindian [AME], European [EUR], and African [AFR]), which was done from 12 loci. MetS diagnosis followed the NCEP-ATPIII criteria. Additionally, the sample was stratified according to the presence or absence of each criterion used for MetS diagnosis (i.e., Type 2 diabetes mellitus (T2DM), hypertension, hypertriglyceridemia, dyslipidemia [low HDL], and central obesity (elevated waist circumference)). Comparisons of genetic ancestry estimates were performed using the Mann-Whitney test, with the significance level set at p < 0.05. The prevalence of MetS was 40.4%. The degree AME, EUR and AFR genetic ancestry was not different between volunteers with or without MetS (p > 0.05). However, AME ancestry was significantly higher among diabetic volunteers (non-diabetics: 13.7% (6.3–35.8) x Diabetics: 26.1% (10.6–48.5); p < 0.05). Community-dwelling old adults with a higher percentage of Amerindian ancestry seem to be prone to T2DM diagnosis.

# 1. Introduction

Metabolic syndrome (MetS) is a group of cardiometabolic risk factors and noncommunicable diseases with a high risk of cardiovascular disease (CVD) (Grundy et al., 2005), being one of the main causes of mortality in the last 20 years (Greenfield and Snowden, 2019). MetS is characterized by a multifactorial nature and genetic ancestry has been associated with many cardiometabolic risk factors and noncommunicable diseases that compound the MetS diagnosis criteria (Soares-Souza et al., 2018; Joseph et al., 2016; Muñoz et al., 2016). In fact, African and Amerindian genetic background appears to have an important role in susceptibility to metabolic diseases (Lins et al., 2012;

# Campbell et al., 2012; Hu et al., 2015; Crowshoe et al., 2018; Gebreab et al., 2015; Mendoza-Caamal et al., 2020).

It is believed that the susceptibility to metabolic diseases associated with African and Amerindian genetic ancestry derives from natural selection, in addition to forced changes in lifestyle (Mendoza-Caamal et al., 2020; Lai et al., 2009; Aguilar-Salinas et al., 2014; Chande et al., 2017), since, historically, in colonized countries, such as Brazil, indigenous people underwent drastic changes in lifestyle, including eating habits (Crowshoe et al., 2018). Latin America has a typical mixed-race population (Norris et al., 2018; Price et al., 2007) and the influence of genetic ancestry as a determinant of health in this population is of particular interest.

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As the genetic background, aging is also a non-modifiable factor that determines many noncommunicable diseases (WHO, 2015), which is particularly relevant for low- and middle-income countries, since the growth rate of the population  $\geq 60$  years old is approximately three times faster in less developed countries than in more developed ones (Chatterji et al., 2015). This justifies the recent interest to investigate the interaction of aging and genetic ancestry to determine clinical outcomes in Brazil, a developing country (Lins et al., 2012).

Lins et al. (2012), investigated the association of serum lipid components and obesity with genetic ancestry in Brazilian old adult women. They concluded that genetic admixture may influence the etiology of lipid metabolism-related diseases and obesity in old adult women, with higher European ancestry associated to obesity, while higher African and Amerindian ancestry associated with abnormal serum lipid profile. Despite this, the Amerindian genetic background has been consistently reported as a determinant of poor glycemic control and Type 2 Diabetes Mellitus (T2DM) (Caro-Gomez et al., 2018; Domínguez-Cruz et al., 2018; Chande et al., 2020), and African genetic ancestry is reported as a determinant of hypertension in the Americas (Zilbermint et al., 2019; Bueno et al., 2020).

Despite the recent increasing interest and knowledge about the interaction between genetic ancestry, aging, and metabolic disorders, there is a gap to be investigated, such as a large study including old adults from both sexes and the analysis of a wide spectrum of metabolic disorders, such as the MetS diagnosis and each component of the MetS diagnostic criteria. Thus, the present study aimed to address these exposed gaps, investigating the relationship between the degree (i.e., percentage) of genetic ancestry and the MetS diagnosis, as well as each component of MetS diagnosis (diabetes mellitus (T2DM), hypertension, hypertriglyceridemia, dyslipidemia (low HDL), increased waist circumference), in community-dwelling Brazilian old adults, a country characterized by a genetically admixed population.

# 2. Methods

# 2.1. Study and sample description

All elderly people ( $\geq$ 60 years) living in the urban area of Aiquara, Bahia, Brazil were invited (home visit) to participate in this study. Two hundred eighty-nine (289) subjects were selected, however, bedridden subjects and/or those with severe cognitive impairment (n = 20) were excluded. In addition, eleven subjects did not consent to the blood withdrawal and ninety-seven (97) had technical problems with their blood samples, limiting gene polymorphism identification and/or diagnosis of MetS. Thus, 161 old adults (64% women) composed the sample of this study. Volunteers were informed about all study procedures and signed an informed consent form. Data were collected between January and July 2015 and all procedures were approved by the local ethics committee in accordance with the Declaration of Helsinki.

# 2.2. Sociodemographic and lifestyle variables

A questionnaire was applied to record the following variables: sex, age, marital status (with a partner or without a partner), self-reported skin color (white, yellow, brown, indigenous and black), in addition to monthly income.

# 2.3. Metabolic syndrome definition

The NCEP-ATP III was used as the criteria for MetS diagnosis, which considers the presence of at least three of the five listed characteristics: abnormal waist circumference (men >102 cm, women >88 cm); hypertriglyceridemia ( $\geq$ 150 mg/dL), low HDL cholesterol (men <40 mg/dL, women <50 mg/dL), hypertension (previous diagnosis or blood pressure  $\geq$ 130/85 mmHg), and high fasting glucose  $\geq$ 110 mg/dL or previous diagnosis of T2DM. Table 1 presents the adopted criteria for

#### Table 1

Adopted criteria	for MetS	diagnosis.	based on	NCEP-ATP	III criteria.

Variable	Cut-off value
Abnormal waist circumference	men >102 cm, women >88 cm
Hypertriglyceridemia	$\geq$ 150 mg/dL
Low HDL cholesterol	men <40 mg/dL, women <50 mg/dL
Hypertension	blood pressure $\geq$ 130/85 mmHg or previous diagnosis of hypertension
High fasting glucose	$\geq$ 110 mg/dL or previous diagnosis of T2DM

# MetS diagnosis.

# 2.4. DNA isolation and genotyping

Venous blood samples (5 ml) were withdrawal and whole blood aliquots were submitted to DNA extraction using the QIAamp DNA Blood Mini Kit (QIAGEN Inc.) according to the procedure provided by the manufacturer. The PCR assays were carried out under specific conditions for each marker. FY-NULL, RB1, LPL, OCA2, CKM, PON1 (rs854560), PON1 (rs662) and DRD2 single nucleotide polymorphisms were identified using PCR-RFLP (Sty I, BamH I, Hae III, Taq I, Hinf I and Bcl, respectively). The Alu and indel insertion polymorphisms: AT3, APOA, PV92 and SB19.3, were also amplified by PCR. Alleles were identified by direct detection on agarose gel after GelRed® staining or polyacrylamide gel after silver nitrate staining.

# 2.5. Determination of genetic ancestry

For individual genetic ancestry estimation, we selected 12 ancestryinformative markers (AIMs) that displayed differential allele frequencies among European, African and Amerindian parental populations. Individual genetic ancestry estimations were performed using the software STRUCUTRE 2.3.4 (Pritchard et al., 2000). Samples from the 1000 Genomes project were used as pseudo-ancestors: 405 Africans (Yoruba in Ibadan, Nigeria, Esan in Nigeria and Mende in Sierra Leone), 207 East Asians (Han Chinese in Beijing and Japanese in Tokyo) and 305 Europeans (Iberian populations in Spain, Toscani in Italy and British in England and Scotland). The East Asian sample was included as a pseudo-ancestor replacing Amerindian, as a Native American population is not represented in the dataset for the selected loci. In this sense, this last population sample was selected, as it presents established similarities of allele frequencies with Amerindians, being an alternative to distinguish Amerindian ancestors from Africans and Europeans in the study sample (Collins-Schramm et al., 2004; Hernandez-Suarez et al., 2014; Mychaleckyj et al., 2017).

# 2.6. Statistical analysis

The prevalence of MetS in the studied population, as well as the prevalence of each component of the MetS diagnosis, were presented as absolute and relative frequency. The Kolmogorov-Smirnov test was used to determine whether the estimates of EUR, AME, and AFR ancestry were normally distributed. Since estimates of EUR, AME, and AFR genetic ancestry were not normally distributed, the Mann-Whitney test was used to compare the estimates of EUR, AME, and AFR ancestry between old adults with and without MetS, as well as with and without each of the components of the MetS diagnosis.

Data were reported as median and interquartile range [Q1-Q3]. Median differences with their respective 95% confidence intervals were reported and used and interpreted as a measure of effect size. This approach allows for identifying the direction and magnitude of the effect, justifying its use as an adequate measure of effect size (Herbert et al., 2011). Aiming to improve the understanding regarding the relationship between the genetic ancestry and each MetS component, the correlation between genetic ancestry and each component of MetS

(Waist circumference, glycemia, blood triglyceride levels, HDL cholesterol, systolic and diastolic blood pressure were taken as continuous data). Spearman's rank correlation coefficient (i.e., Spearman's rho coefficient) and its respective p-value were obtained. Spearman's rank correlation coefficient was chosen because estimates of EUR, AME, and AFR genetic ancestry were not normally distributed. All analyses were performed using the IBM SPSS V.21.0 software (SPSS, IBM Corporation, Armonk, New York, USA), and the significance level was set at  $p \leq 0.05$  for all inferential tests.

# 3. Results

The median age of the studied sample was 72.0 [66.0–78.0] years old. Regarding marital status, 79.5% reported having a partner, and 52.8% self-reported as brown, 35.4% black, 8.1% white, 1.9% yellow, and 1.9% indigenous. The prevalence of MetS in the studied population was 40.4%, while the prevalence of T2DM, hypertriglyceridemia, SAH, central obesity, and dyslipidemia were 31.1%, 29.8%, 68.9%, 42.7%, 45.9%, respectively. The median monthly income of the studied population was R\$ 937.00 [930.00–937.00]. Stratifying the sample by MetS diagnosis, there was no significant difference in monthly income between those with (R\$ 937.00 [920.00–937.00]) and without MetS (R\$ 937.00 [932.00–937.00]).

The estimates of genetic ancestry generated for the studied sample show values consistent with a genetic admixed-population based on a tri-hybrid model (EUR = 43.3 % [16.9–73.0], AFR = 13.7 % [3.6–41.5] and AME = 18.6 % [8.0–44.2]), as expected for the Brazilian population. When stratified by MetS diagnosis, no significant difference was observed in the estimated EUR, AME and AFR ancestry between old adults with and without MetS (Median difference [CI 95%]: AME = -0.20% [-5.9 to 5.0]; EUR = 1.10% [-7.6 to 10.5]; AFR = -1.60% [-5.3 to 1.7]). Among the components of the MetS diagnostic criteria, only T2DM showed a significant difference in the estimation of AME ancestry, where diabetic old adults exhibited a higher percentage of AME ancestry (EAS = -6.3% [-14.0 to -0.2]). The comparisons of estimates of AME, EUR, and AFR genetic ancestry of the old adults stratified by each studied outcome are shown in Table 2.

The Spearman's rho coefficients demonstrated a positive and significant correlation between the estimate of AME genetic ancestry and glycemia (Spearman's rho = 0.166; p = 0.03). The estimate of EUR genetic ancestry was negative and significantly correlated to systolic blood pressure (Spearman's rho = -0.166; p = 0.04). Table 3 presents Spearman's rho coefficients for all pairwise correlations.

# 4. Discussion

The present study aimed to evaluate the relationship between the degree of genetic ancestry (European, African, and Amerindian) with the Metabolic Syndrome (MetS) diagnosis and its diagnostic components separately, in community-dwelling old adults. We found that the old adults from the region studied (i.e., south center Bahia, Brazil) presented a predominant European genetic ancestry, followed by the AME and AFR genetic ancestry. The estimates observed in our study were consistent with those reported in previous studies for Brazilians, despite the use of different sets of genetic markers (Lins et al., 2012). The main finding of this study was those diabetic old adults exhibited a higher degree of AME genetic ancestry.

Brazil is a country characterized by great miscegenation and as expected, European ancestry was predominant in our studied sample. Pena et al. (2020) contextualize the large immigration from Europe to Brazil between the 19th and 20th centuries, which explains the predominance of the genetic ancestry of European heritage. Despite this higher percentage of European genetic ancestry, our results do not allow us to associate this genetic ancestry with a greater predisposition to the studied clinical outcomes. In fact, a wide scientific literature suggests that African and Amerindian ancestry is associated with a greater

# Table 2

Genetic ancestry estimates from older adults stratified by metabolic syndrome (MetS) diagnosis and its individual components (T2DM, hypertension, hypertriglyceridemia, dyslipidemia, and central obesity).

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	MetS		Median difference (IC95%)		
	_	+			
AME (%)	19.0 (8.2–43.0)	18.4 (7.9–45.0)	-0.20 (-5.9 to 5.0)		
EUR (%)	44.4 (19.5–76.3)	42.7 (14.4–67.1)	1.10 (-7.6 to 10.5)		
AFR (%)	12.0 (3.1–42.3)	16.2 (6.0–35.2)	-1.60 (-5.3 to 1.7)		
	T2DM	+	Median difference (IC95%)		
AME (%)	13.7 (6.3–35.8)	26.1 (10.6-48.5)	-6.3 (-14.0 to -0.2)*		
EUR (%)	50.6 (19.5–77.0)	39.4 (16.7–65.8)	5.1 (-4.6 to 15.8)		
AFR (%)	14.7 (3.4–43.8)	13.0 (4.1–35.2)	-1.60 (-3.5 to 4.6)		
	Hypertension		Median difference (IC95%)		
		+			
AME (%)	19.1 (8.0–46.6)	18.5 (8.1–41.6)	1.6 (-3.9 to 7.8)		
EUR (%)	36.4 (21.8-69.5)	48.0 (14.6–74.0)	-0.9 (-11.5 to 8.0)		
AFR (%)	14.5 (3.0–41.5)	13.7 (4.1–40.8)	-0.7 (-4.6 to 3.3)		
	Hypertriglyceridemia		Median difference (IC95%)		
		+			
AME (%)	16.1 (8.0-42.0)	28.4 (7.1–45.3)	-3.1 (-11.5 to 2.8)		
EUR (%)	41.4 (19.7–76.9)	49.2 (14.7-66.5)	0.3 (-9.6 to 10.5)		
AFR (%)	AFR (%) 15.6 (3.6–44.8) 13.0 (3.8–28.8)		0.7 (-2.6 to 6.9)		
	Low HDL		Median difference (IC95%)		
		+			
AME (%)	17.3 (6.3–39.2)	18.5 (9.3–45.2)	-1.6 (-7.4 to 3.2)		
EUR (%)	48.0 (19.9–76.8)	41.8 (15.6–66.7)	2.7 (-5.7 to 12.4)		
AFR (%)	7.6 (2.9–41.8)	17.5 (6.1–37.1)	-2.2 (-7.1 to 0.8)		
	Waist circumference		Median difference (IC95%)		
		+			
AME (%)	17.9 (9.1–42.0)	24.5 (9.3–45.2)	-1.5 (-8.7 to 4.3)		
EUR (%)	45.6 (16.7–78.1)	50.4 (21.8–70.8)	-1.4 (-10.8 to 8.3)		
AFR (%)	13.3 (3.3-40.1)	9.8 (4.1–33.5)	0.5 (-2.8 to 5.4)		

T2DM = Type 2Diabetes Mellitus; AME: Amerindian ancestry; EUR: European ancestry; AFR: African ancestry. (–) without outcome; (+) with outcome; (\*) Significantly different at p < 0.05.

predisposition to various cardiovascular diseases (Muñoz et al., 2016; Lins et al., 2012; Campbell et al., 2012; Hu et al., 2015; Crowshoe et al., 2018; Gebreab et al., 2015; Mendoza-Caamal et al., 2020).

MetS is a multifactorial clinical condition, including several cardiovascular risk factors and comorbidities, which are known to be associated with the genetic background. In fact, there is evidence that MetS manifests itself differently according to the ancestral groups (Gurka et al., 2014). In the present analysis, we observed that the proportion of EUR, AME or AFR genetic ancestry was not related to the MetS diagnosis, although it was related to the T2DM diagnosis, one of the diagnostic components of MetS.

Although both, diabetic and non-diabetic old adults exhibited a high European genetic ancestry, the proportion of AME ancestry was significantly higher among diabetic old adults compared to non-diabetic ones. Previous studies carried out in populations in the Americas support this association. Caro-Gomez et al. (2018) suggest the presence of a subtle effect of the Native American genetic heritage on the risk of low β-cell function, one of the characteristic traits of T2DM, and observed in the Colombian population (Caro-Gomez et al., 2018). On the other hand, Domínguez-Cruz et al. (2018) showed that the analysis of the genetic population structure was not different between T2DM and healthy individuals in the Mayan population of Mexico. Chande et al. (2020) also indicated that the genetic risk of T2DM in Hispanic/Latino populations from Colombia and the United States of America is positively correlated with African and Native American ancestry and negatively correlated with European ancestry. Thus, the higher proportion of AME ancestry observed among diabetic old adults in our study corroborates these

#### Table 3

Spearman's rho coefficients for each	pairwise correlation between	estimates of AME, EUR, A	R genetic ancestr	v and components of MetS.

	AME		EUR	EUR		AFR	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	
Waist circumference	0.068	0.40	0.022	0.78	-0.024	0.76	
Glycemia	0.166*	0.03	-0.100	0.20	0.019	0.81	
Blood triglyceride levels	0.112	0.16	-0.069	0.38	-0.003	0.97	
HDL cholesterol	-0.100	0.20	0.109	0.17	-0.087	0.27	
Systolic blood pressure	-0.015	0.85	-0.166*	0.04	0.124	0.12	
Diastolic blood pressure	-0.019	0.81	-0.018	0.82	0.051	0.53	

(\*) Statistically significant at p < 0.05.

previous studies carried out in Colombian, Mexican, and North American populations.

Despite hypertension, hypertriglyceridemia, low HDL, and obesity representing clinical outcomes with a recognized genetic heritability influence (Rankinen et al., 2015), no significant relationship was found between the three ancestral components (i.e., AME, EUR and AFR). Despite this, Keaton et al. (2021) demonstrated that GBR (European) ancestry was negatively associated with hypertension, representing a protective factor against hypertension, while YRI (African) ancestry was positively associated with hypertension, as well as the risk of hypertension and the risk of drug-resistant hypertension. In our study, no significant differences were observed in the estimate of EUR, AME, or AFR genetic ancestry between hypertensive and non-hypertensive old adults. Noteworthy, we found a negative association between systolic blood pressure and the estimate of EUR genetic ancestry, corroborating the protective hypothesis pointed out previously by Keaton et al. (2021). However, the comparison of the percentage of EUR genetic ancestry between hypertensive and normotensive old adults did not indicate a significant difference. It is important to note that the blood pressure measure could be influenced by antihypertensive drugs, which could influence the correlation parameters, especially because the prevalence of hypertension is high among older adults. Additionally, the sample was stratified as hypertensive or normotensive based on blood pressure and the self-reported diagnosis (as foreseen in the diagnostic criteria) for comparison procedures, which is not influenced by antihypertensive drugs.

No significant difference was also observed in the estimate of genetic ancestry between the old adults with and without central obesity and dyslipidemia (hypertriglyceridemia and low HDL, respectively), despite previous evidence of an association between these outcomes and groups of different ethnic/racial aspects (Raygor et al., 2019; Lim et al., 2019).

The association of genetic ancestry and cardiovascular risk factors should always be analyzed considering the history of the social construction involved in a country/community, since the great migrations that occurred at different times in human history led to different ethnic admixtures around the world (Benton et al., 2021; Riyaz et al., 2018). Climatic differences and, especially, dietary differences imposed by migrations culminate in metabolic alterations in organisms genetically adapted by years of exposure to the same dietary pattern (Benton et al., 2021; Riyaz et al., 2018). This hypothesis supports the understanding of the association between African and Amerindian ancestry and several cardiovascular risk factors in countries that have gone through a colonization process (Mendoza-Caamal et al., 2020; Aguilar-Salinas et al., 2014; Hu et al., 2015), with an increase in calorie consumption being observed, especially based on fats and simple sugars, as major changes in eating habits (Aguilar-Salinas et al., 2014).

Our results indicated a significant relationship only between AME ancestry and the T2DM diagnosis, which can be explained by the characteristics and genetic components of the population studied here. In our study, we investigated old adults from a region with a demographic history of indigenous ethnicity (Pataxó, Mongoyó and Ymboré) (Paraiso, 1982; Oliveira, 2012) and Italian ethnicity (Santos, 1956; Oliveira, 2012). Additionally, due to its historical context, the state of Bahia

received a large contingent of enslaved Africans, especially from the regions such as Senegal, Angola, Mozambique, and Ethiopia (Tavares, 2001), but their distribution throughout the state does not seem to be homogeneous, since it was concentrated in coastal areas (Tavares, 2001), justifying the lower proportion of African ancestry in our studied sample, since the municipality of Aiquara is located in the interior (south center) of the state of Bahia, 402 km from the capital (Salvador), which was the main point landing of enslaved Africans in Brazil.

The municipality of Aiquara began to be populated around 1916 when some families settled on land donated by Preguiça's farm, in the territory that belonged to the municipality of Jequié (Aiquara, 2018). Thus, its development was supported by commerce, owing to the traffic of troops and herds from the north of Minas Gerais toward Salvador (Araújo, 1971). This context favored a large group of people, including Italian peddlers, to settle there (Santos, 1956). There are reports and historical documents showing the presence of indigenous tribes, such as Pataxó, Mongoyó and Ymboré, forging a broad ethnic group in the South Center of Bahia territory to which Aiquara belongs (Paraiso, 1982; Oliveira, 2012; Rocha, 2018).

It is important to emphasize that the municipality studied has a low human development index (0.583) and the monthly income reported by the volunteers confirms the context of a low-income population, which predisposes it to worse health conditions. In fact, the monthly income of the population studied was quite homogeneous, with no significant difference in the median monthly income between the old adults with and without MetS, indicating that this social aspect does not seem to be associated with the diagnosis of MetS in the studied population. On the other hand, genetic admixture influences allele frequencies in a population, which in turn helps to clarify the observed differences in the epidemiology of some diseases in the mixed-race population. The sample loss due to technical problems could be pointed out as a limitation of our study. Further studies could develop strategies to avoid this limitation.

Our results indicate that a higher percentage of AME ancestry is related to the prevalence of T2DM in the studied community-dwelling old adults, which was confirmed by the significant correlation between the percentage of AME ancestry and the glycemia. Despite reports in the literature of the influence of genetic ancestry on MetS in several populations, this relationship was not identified in our sample, and the fact we included only old adults could influence this finding since the aging process leads to homeostasis impairments independently of genetic ancestry.

# 5. Conclusion

Our results indicated no difference in the estimates of genetic ancestry (European, Amerindian and African) between old adults with and without MetS, while significantly higher estimates of Amerindian ancestry was found in old adults with T2DM when compared to those without T2DM.

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# Author's CRediT statements

Jamille Silva Oliveira: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Visualization. Gabriel Novaes Miranda: Formal Analysis, Writing – Review & Editing. Ícaro JS Ribeiro: Methodology, Formal Analysis, Writing – Review & Editing. Ivna Vidal Freire: Formal Analysis, Writing – Review & Editing. Cezar A. Casotti: Formal Analysis, Writing – Review & Editing, Project Administration. Ana Angélica Leal Barbosa: Formal Analysis, Writing – Review & Editing. Rafael Pereira: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization, Project Administration.

# Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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