

## Dyslipidemia and the risk of incident hypertension in a population of community-dwelling Brazilian elderly: the Bambuí Cohort Study of Aging

Dislipidemia e risco de incidência de hipertensão em uma população de idosos brasileiros vivendo em comunidade: Estudo de Coorte de Idosos de Bambuí

Marco Polo Dias Freitas <sup>1,2</sup>  
 Antônio Ignácio de Loyola Filho <sup>2,3</sup>  
 Maria Fernanda Lima-Costa <sup>2</sup>

### Abstract

*This study aimed to examine the prognostic value of lipid parameters for incident hypertension in elderly living in a community. The study included 306 (81% from total) persons aged  $\geq 60$  years who were free of hypertension and of cardiovascular diseases at the baseline survey of the Bambuí Cohort Study of Aging. The cumulative incidence of hypertension over three years was 37.3%. The relative risk (RR) of incident hypertension decreased 0.92 for each unit of HDL-cholesterol (95%CI: 0.86-0.99) independent of several potential confounding factors. Individuals with HDL-cholesterol in the top tercile ( $\geq 55\text{mg/dL}$ ) had a risk of hypertension halve that those in the bottom tercile (RR = 0.54; 95%CI: 0.33-0.90). Other lipid parameters had no significant effect on the outcome. High HDL-cholesterol showed an independent protective effect on subsequent development of hypertension in the elderly.*

*Dyslipidemias; Hypertension; Aged; Cohort Studies*

### Introduction

Arterial hypertension is the principal risk factor for mortality and the second leading cause of disability adjusted life years around the world <sup>1,2</sup>. The risk of developing arterial hypertension increases markedly with age <sup>3,4</sup>, and is the most common chronic disease in the elderly, with prevalence of about 60% in Latin America and the Caribbean <sup>5</sup>, as well as in the town of Bambuí, Minas Gerais State, Brazil <sup>6</sup>. Populations in these countries are aging fast <sup>7</sup> and unless effective primary and secondary prevention measures are implemented, this demographic change will bring about a significant increase in the burden of arterial hypertension in this region of the world.

Hypertension and dyslipidemia are widely recognized risk factors for cardiovascular disease <sup>2,8</sup>. And yet, the pathophysiology of the association between hypertension and dyslipidemias is still not completely understood <sup>9</sup>. Several mechanisms have been postulated to explain this association. Atherosclerosis – caused in great part by dyslipidemias <sup>9</sup> – leading to structural changes that result in the decreased elasticity of large arteries, is generally viewed as the principal pathophysiologic alteration contributing to the emergence of arterial hypertension in the elderly <sup>10</sup>. By altering vasomotor mechanisms mediated by nitric oxide, dyslipidemias also alter endothelial function <sup>11</sup>, which in turn can cause increases in blood pressure. Renal microvascular

<sup>1</sup> Hospital Universitário de Brasília, Universidade de Brasília, Brasília, Brasil.  
<sup>2</sup> Núcleo de Estudos em Saúde Pública e Envelhecimento, Fundação Oswaldo Cruz/Universidade Federal de Minas Gerais, Belo Horizonte, Brasil.  
<sup>3</sup> Escola de Enfermagem, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil.

#### Correspondence

M. P. D. Freitas  
 Centro de Medicina do Idoso,  
 Hospital Universitário de Brasília, Universidade de Brasília.  
 SGAN 605, Brasília, DF  
 70840-901, Brasil.  
 marcopolo.freitas@gmail.com

injuries due to dyslipidemias are also postulated to contribute to arterial hypertension<sup>12</sup>. Finally, coincident genetic factors, such as having chromosomal regions related to blood pressure and dyslipidemias in common<sup>13,14</sup>, which predispose for the concomitant occurrence of hypertension and dyslipidemia<sup>15</sup>, and the fact that reductions in blood pressure in hypertensive individuals have been attributed to use of statins<sup>16</sup>, suggest shared pathophysiologic mechanisms that need to be better elucidated.

Several studies have examined prospectively whether elevated lipid levels are associated with the subsequent development of hypertension in middle age adults. In most studies, high-density lipoprotein cholesterol (HDL-C) levels show an independent and inverse association with incident hypertension<sup>17,18,19,20,21</sup>. Higher levels of triglycerides<sup>18,20,22</sup>, higher total cholesterol (total-C)<sup>19,21</sup>, higher non-HDL cholesterol (non-HDL-C)<sup>19,21</sup>, and higher levels of low density lipoprotein cholesterol (LDL-C)<sup>17,20</sup> have been found to be associated with an increased risk of hypertension in some studies, but not in all. Nevertheless, the findings of these studies are not entirely comparable, as the participants of the various cohorts differed in terms of age, gender (some studies included only men and others only women), socioeconomic status, ethnicity and the way in which information about hypertension was obtained (self-reported or objective measure), among other relevant aspects.

Moreover, the role of dyslipidemia in predicting hypertension in the elderly has received little attention. To our knowledge, a single previous cohort study on the issue was carried out in the elderly<sup>23</sup>. This study followed 187 initially non-hypertensive elderly; over an eight year follow-up period there were 44 incident cases. HDL-C had a protective effect on the incidence of hypertension (univariate relative risk – RR = 0.8 per 5mg/dL; 95% confidence intervals – 95%CI: 0.42-1.0).

We used data from three years of follow-up of the Bambuí Health and Aging Study to examine whether lipid parameters predict subsequent development of hypertension in old age.

## Methods

### Study design and population

The study was conducted in Bambuí, a town of approximately 15,000 inhabitants, located in the state of Minas Gerais, in Southeastern Brazil. Enrollment and monitoring procedures of the Bambuí Cohort Study of Aging have been described in

detail elsewhere<sup>6,24</sup>. Briefly, the baseline cohort population consisted of all residents aged 60 and over on January 1<sup>st</sup>, 1997 who were identified by means of a complete census in the city. Baseline data collection was performed from February to May, 1997, including standardized interviews, blood tests and blood pressure measurements, among others. Blood pressure measures were repeated in the third wave, which was conducted from March to June, 2000.

All cohort participants who were free of hypertension at baseline (as defined below) and who did not have cardiovascular diseases were eligible for inclusion. Cardiovascular diseases that prompted exclusion were: prior medical diagnosis of myocardial infarction, symptoms of angina pectoris or intermittent claudication<sup>25</sup>, stroke<sup>26</sup> and congestive heart failure. The presence of congestive heart failure was objectively defined by a plasma B-type brain natriuretic peptide (BNP) level > 100pg/mL (MEIA/AxSYM; Abbott, Abbott Park, USA), as recommended by the manufacturer, and QRS interval ≥ 120ms on ECG<sup>27</sup> (Hewlett Packard M1700A; Hewlett Packard, Palo Alto, USA).

### Definition and measurement of blood pressure

Three measures of blood pressure were obtained at least two minutes apart. The mean of the second and third measures was used following a standard protocol<sup>28</sup>. Blood pressure was measured in the project field study clinic in the early morning, at least 30 minutes after consumption of caffeine and/or use of tobacco and after five minutes of rest. Measurements were taken on the right arm with an appropriate size cuff, using a random zero Mercury sphygmomanometer (Tycos 5097-30; Tycos, Arden, USA) and stethoscope (Littmann Cardiology II; 3M, St. Paul, USA). Systolic and diastolic blood pressures were registered using as a reference the first and the fifth Korotkoff sounds, respectively. The technicians that measured blood pressure were certified after training at a specialized center at the School of Medicine of the Minas Gerais Federal University (Faculdade de Medicina, Universidade Federal de Minas Gerais). The same procedures were used at baseline and during the third year of follow-up.

The use of medications was measured by mean of verifying the packaging and/or the physician's prescription during home visits that were conducted with all participants. Medications were coded according to the Anatomical Therapeutic Chemical Index (ATC/DDD Index)<sup>29</sup> and were considered antihypertensives if they were

classified in groups ATC: C02 – antihypertensives, C03 – diuretics, C07 – beta-blockers, C08 – calcium channel blockers, and C09 – agents that act on the renin-angiotensin system.

Arterial hypertension was defined in this study as the presence of systolic blood pressure equal or higher than 140mmHg or diastolic blood pressure equal or higher than 90mmHg or treatment for hypertension<sup>30</sup>. We considered incident cases those individuals that were free of hypertension at baseline and were found to be hypertensive at the third follow-up visit in 2000.

### Lipids dosages

Blood specimens for biochemical assays were collected after a recommended 12 hour fast. Serum levels of total-C, HDL-C and triglycerides were determined by enzymatic methods, using standard assay kits (Boehringer Mannheim; Ingelheim am Rhein, Germany). All the measures were performed using an automated analyzer (Eclipse Vitalab, Merck, Schiphol-Rijk, Netherlands) at the study's central laboratory at the René Rachou Research Center of the Oswaldo Cruz Foundation (Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz – CPqRR/Fiocruz). Details are available from other publications<sup>6,24</sup>. For the present analysis the following lipid parameters were considered: total-C, HDL-C, non-HDL-C, total-C/HDL-C ratio and triglycerides.

### Other measures

Other baseline measures considered in this study included: age, sex, schooling level (number of complete years of schooling), smoking, physical activities during leisure time, alcohol consumption (weekly frequency in previous 12 months), parental history of cardiovascular diseases (history of myocardial infarction, angina pectoris, hypertension and/or stroke), waist circumference, and fasting blood glucose. Current smokers were those who had smoked at least 100 cigarettes in the lifetime and were still smokers. "No physical activities during leisure time" was defined by the absence of any exercise lasting 20-30 minutes in the previous 90 days. Measures of waist circumference were performed using a flexible inelastic tape measure, with this subject standing.

None of the participants had a history of drug treatment for lowering lipids, and none had used these drugs during the period in which patients were followed. Thus, drugs for lowering cholesterol were not included in the present analysis.

### Statistical analyses

The univariate data analysis was based on Pearson's chi square, Student's t and Mann-Whitney rank sum tests to assess statistical significance of differences between frequencies, means and medians, respectively. The multivariate analyses of predictors of incident hypertension were based on RR and 95%CI estimated by Poisson regression. Separate multivariate analyses were performed for each lipid parameter; these were categorized in increased units of ten percentiles. The relative risks were incrementally adjusted for age (continuous), sex, and schooling level (model 1), smoking, physical activity and alcohol consumption (model 2), parental history of cardiovascular diseases, waist circumference (continuous), blood glucose in log values (continuous) (model 3) and systolic blood pressure (model 4). A complementary multivariate analysis was implemented based on categorical values of HDL-C to assess its association with incident hypertension. The significance of multiplicative interactions between HDL-C with age or sex on the outcome was examined by using cross-product terms in Poisson regression models. Statistical analyses were conducted using Stata 11.0 statistical software (Stata Corp., College Station, USA). All p-values were 2-tailed ( $\alpha = 0.05$ ).

The Bambuí cohort study was approved by the Ethics Research Committee of Fiocruz. Participants signed an informed consent at enrollment and at each follow-up visit.

### Results

Of 1,742 Bambuí residents aged 60 years and over, 1,494 (85.8%) had had their blood pressure measured at baseline. Of these, 464 were classified as non-hypertensive. Eighty-five with existing cardiovascular disease were excluded. Of the 379 eligible elderly, 306 had a blood pressure measure recorded at the third year of follow-up and constitute the population base for this study. The other 73 included 55 who had died and 18 who had emigrated or declined to participate.

The baseline characteristics of study participants are shown in Table 1. Mean age was 68.0 (standard deviation – SD = 6.7) years and women (54.2%) outnumbered men. The number of years of formal schooling was very low: 62.4% had completed less than four years of school. The mean (SD) levels total-C, HDL-C, non-HDL-C, total-C/HDL-C ratio were 230.3mg/dL (49.4), 50.0mg/dL (13.8), 180.3mg/dL (49.8) and 4.9mg/dL (1.7), respectively. The median

Table 1

Baseline characteristics of study participants. The Bambuí Cohort Study of Aging.

Characteristics	% or mean (SD) or median (IQR) (N = 306)
Total cholesterol in mg/dL [mean (SD)]	230.3 (49.4)
HDL cholesterol in mg/dL [mean (SD)]	50.0 (13.8)
Non-HDL cholesterol in mg/dL [mean (SD)]	180.3 (49.8)
Total cholesterol / HDL cholesterol ratio [mean (SD)]	4.9 (1.7)
Triglycerides in mg/dL [median (IQR)]	115.5 (84-161)
Age [mean (SD)]	68.0 (6.7)
Female sex (%)	54.2
Less than 4 years of schooling (%)	62.4
Current smoking (%)	18.6
Absence of physical activities during leisure times in previous 90 days * (%)	23.1
Alcohol consumption: 1-6 drinks a week in previous 12 months (%)	5.2
Parental history of cardiovascular diseases < 50 years (%)	23.9
Waist circumference in centimeters [mean (SD)]	88.3 (10.3)
Blood glucose in mg/dL, [geometric mean (SD)]	96.0 (88-106)
Systolic blood pressure in mmHg [mean (SD)]	120.7 (12.1)
Diastolic blood pressure in mmHg [mean (SD)]	75.8 (8.4)

IQR: interquartile range; SD: standard deviation.

\* Exercises for 20-30 minutes less than 3 times a week;

Table 2

Univariate analysis of the association between baseline characteristics and incident hypertension. The Bambuí Cohort Study of Aging.

Baseline characteristics	Incident hypertension		p-value *
	Yes (n = 114)	No (n = 192)	
	% or mean (SD)	% or mean (SD)	
Total cholesterol in mg/dL [mean (SD)]	229.7 (51.8)	230.7 (48.1)	0.861
HDL cholesterol in mg/dL [mean (SD)]	46.7 (12.4)	52.0 (14.2)	0.001
Non-HDL cholesterol in mg/dL [mean (SD)]	182.9 (53.2)	178.7 (47.7)	0.474
Total cholesterol/HDL cholesterol ratio [mean (SD)]	5.3 (1.9)	4.7 (1.5)	0.006
Triglycerides in mg/dL [median (IQR)]	122.5 (86-156)	110 (82-161)	0.380
Age [mean (SD)]	67.7 (6.6)	68.3 (6.8)	0.516
Female sex (%)	54.2	57.0	0.454
Less than 4 years of schooling (%)	62.0	61.4	0.778
Current smoking (%)	21.0	17.2	0.401
Absence of physical activities during leisure times in previous 90 days (%)	86.0	74.0	0.014
Alcohol consumption: 1-6 drinks a week in previous 12 months (%)	6.1	4.7	0.581
Parental history of cardiovascular diseases < 50 years (%)	21.1	15.6	0.229
Waist circumference in centimeters [mean (SD)]	89.8 (11.0)	87.4 (9.9)	0.051
Blood glucose in mg/dL [median (IQR)]	98 (90-107)	95 (87-105)	0.167
Systolic blood pressure in mmHg [mean (SD)]	124.4 (10.9)	118.5 (12.3)	< 0.001
Diastolic blood pressure in mmHg [mean (SD)]	78.2 (8.2)	74.3 (8.3)	< 0.001

IQR: interquartile range; SD: standard deviation.

\* p-value: Pearson's chi square, Student's t and Mann-Whitney rank sum tests for differences between frequencies, means and medians, respectively.

triglyceride level was 115.5mg/dL (interquartile range – IQR = 84–161).

The cumulative incidence of hypertension over three years was 37.3%. Results of the univariate analysis of factors associated with the development of hypertension are presented in Table 2. Statistically significant ( $p < 0.05$ ) associations with incident hypertension were observed for total-C/HDL-C ratio, HDL-C, absence of physical activity during leisure time, systolic blood pressure, and diastolic blood pressure. Waist circumference was at the borderline of the statistical significance. Other variables did not reach statistical significance in this analysis.

After adjustments for potential confounding variables (Table 3), there was a significant association between decreased HDL-C level and incident hypertension (fully adjusted RR = 0.92; 95%CI: 0.86–0.99). A significant relative risk was also observed for Total-C/HDL ratio in the analysis adjusted by socio-demographic variables, but this association disappeared after adjustments for lifestyle and other relevant characteristics. Total-C, non-HDL-C and triglycerides were not found to be associated with the risk of hypertension in any of the multivariate models.

A HDL-C level in the top tercile (55mg/dL and over) in comparison with the bottom tercile showed an independent and protective effect for incident hypertension (fully adjusted RR = 0.54; 95%CI: 0.33–0.90) (Table 4). No significant effect modifiers between age and sex on the association between HDL-C and incident hypertension ( $p$ -value for interaction = 0.249 for age and 0.738 for sex) was found.

## Discussion

This study provides epidemiological evidence of a protective effect of HDL-C level on the risk of hypertension in an elderly population initially free of cardiovascular diseases. This association persisted after adjustments for several potential confounding variables, including baseline systolic blood pressure level, and suggests a graded effect. Low HDL-C appears to precede the development of hypertension by at least three years.

Population-based studies of the incidence of arterial hypertension in Brazil are rare. To our knowledge there is only one population-based cohort study of middle-aged individuals on this issue. This study was conducted in the city of Porto Alegre, Rio Grande do Sul State, South of Brazil<sup>31</sup>. Among 589 normotensive individuals (mean age = 39 years), 127 (21.6%) developed arterial hypertension after a mean follow-up of 5.6 years. After adjustments for relevant characteristics, age and waist/height ratio were the only factors that remained significantly associated with the incidence of arterial hypertension. The present study was conducted in an older community-based cohort (mean age = 68 years). The 3-year incidence of hypertension was higher (37.3%) than that of the above mentioned study, but similar to that observed among elderly participants of the Framingham Study cohort, over the course of four years of follow-up<sup>32</sup>.

HDL-C levels are importantly affected by age, and a protective effect of increased HDL-C level on incident hypertension in the elderly is plausible. Longitudinal studies have shown that there is a decline in serum HDL-C levels with increasing age<sup>33,34</sup>, while in cross-sectional stud-

Table 3

Multivariate-adjusted relative risks (RR) and 95% confidence intervals (95%CI) for ten percentile unit increments in each lipid parameter. The Bambuí Cohort Study of Aging.

Baseline lipid parameter	Model 1	Model 2	Model 3	Model 4
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Total cholesterol	0.98 (0.91–1.04)	0.98 (0.91–1.04)	0.97 (0.91–1.04)	0.97 (0.91–1.04)
HDL cholesterol	0.92 (0.86–0.98) *	0.92 (0.86–0.98) *	0.93 (0.87–0.99) *	0.92 (0.86–0.99) *
Non-HDL cholesterol	1.00 (0.86–0.98)	1.00 (0.94–1.07)	1.00 (0.93–1.07)	0.99 (0.93–1.06)
Total cholesterol/HDL cholesterol ratio	1.06 (1.00–1.13) *	1.06 (0.99–1.12)	1.04 (0.97–1.12)	1.05 (0.98–1.12)
Triglycerides	1.02 (0.95–1.09)	1.02 (0.96–1.09)	1.01 (0.94–1.08)	1.01 (0.94–1.08)

Model 1: adjusted for age, sex, and schooling; Model 2: adjusted for the variables in Model 1 and smoking, physical activity, and alcohol consumption; Model 3: adjusted for the variables in Model 2 and parental history of cardiovascular diseases, waist circumference, and blood glucose; Model 4: adjusted for the variables in Model 3 and systolic blood pressure.

\*  $p$ -value < 0.05 (Wald's test).

Table 4

Multivariate-adjusted relative risks (RR) and 95% confidence intervals (95%CI) for incident hypertension, by baseline HDL cholesterol level. The Bambuí Cohort Study of Aging.

Baseline HDL cholesterol in mg/dL	RR (95%CI) *	p-value **
< 43 (bottom tertile)	1.00	
44-54	0.75 (0.49-1.15)	0.191
≥ 55 (top tertile)	0.54 (0.33-0.90)	0.018

\* Relative risk and 95% confidence intervals estimated by Poisson regression and adjusted for age, sex, schooling, current smoking, physical activities, alcohol consumption, parental history of cardiovascular diseases, waist circumference, blood glucose and systolic blood pressure;

\*\* p-value: Wald's test.

ies, serum HDL-C levels tend to remain stable or increase slightly<sup>33</sup>, suggesting that individuals whose HDL-C levels remain high are more likely to survive. A decline in HDL-C concentration and function may occur secondary to hormonal changes, inflammatory processes, and diabetes mellitus. Beyond these effects, specific aging processes may be involved<sup>35</sup>. In a meta-analysis of 61 prospective studies, mostly in Western Europe and North America, the association of age, gender, and blood pressure with total-C, HDL-C and LDL-C, was evaluated in relation to cardiovascular mortality. Low HDL-C was identified as a strong and independent predictor of mortality from ischemic heart disease, both in middle age and in the elderly<sup>36</sup>.

Low serum HDL-C levels contributed to structural and functional alterations which led to arterial rigidity<sup>35</sup>. Studies carried out in animal models<sup>37</sup> and humans<sup>38</sup> showed that low HDL-C levels are associated with significant endothelial dysfunction and compromised peripheral vasodilatation. In autopsies of elderly Japanese women, it was observed that serum HDL-C levels were inversely associated with atherosclerosis of medium and large arteries<sup>39</sup>. Epidemiologic studies involving elderly and middle age individuals demonstrated an inverse relationship between serum HDL-C levels and arterial rigidity<sup>40,41,42</sup>. The hardened arteries, in turn, lead to an increase in the speed of return of arterial pressure waves reflected from the peripheral circulation, so that there is an increase in peak systolic blood pressure<sup>10,43</sup>. Added to this, increased blood pressure

itself can intensify arterial stiffening and compromise endothelium-dependent vasodilatation<sup>44</sup>. In one of the analyses of the Framingham Heart Study, Franklin et al.<sup>45</sup> showed that the continuous increase in systolic blood pressure after 60 years of age has a strong relationship with the increasing in large artery stiffness and that even a high normal systolic blood pressure may intensify the arterial rigidity, resulting in a vicious cycle that culminates in arterial hypertension. It seems that is atherosclerosis, provoked in great part by the dyslipidemia<sup>9</sup>, promotes structural and functional alterations that result in reduced elasticity of the large arteries: principal pathophysiologic alteration of the emergence of arterial hypertension in the elderly<sup>10</sup>.

Strengths of this study include the community-based sample, the standardized and systematic measures of parameters at baseline, standardized blood pressure measures at baseline and at follow-up, and minimal loss of participants to follow-up. This allowed a meaningful estimate of a three-year accumulative risk of hypertension. This study has some limitations. There were only 114 incident cases of hypertension among cohort members. This potentially limits the statistical power to detect small effects in our analysis. Because blood pressure measurements were performed in a single day, our results are subject to effects of regression to the mean, which would tend to underestimate the strength of the associations found. Residual confounding is a possibility. Nevertheless, we were able to adjust relative risks for socio-demographic variables and traditional cardiovascular risk factors. Observer bias is unlikely because blood pressure measures and lab tests were performed independently, and without knowledge of the respective results.

Lower serum levels of HDL-C went unrecognized as a predictor of subsequent hypertension for a long time. Only recently has evidence emerged from cohort studies indicating an inverse association between HDL-C and incident hypertension in middle-aged<sup>17,18,19,20,21</sup> and older<sup>23</sup> persons in North America and/or Western Europe. Our study extends this observation to a Brazilian elderly population. The consistency of this association suggests that HDL-C measurements may be useful to identify persons at increased risk of hypertension in primary care settings for prevention.

## Resumo

*O objetivo do estudo foi examinar o valor prognóstico de parâmetros lipídicos para a incidência de hipertensão arterial em idosos vivendo na comunidade. A pesquisa incluiu 306 (81% do total) pessoas com idade  $\geq 60$  anos que estavam livres de hipertensão e de doenças cardiovasculares na linha de base do Estudo de Coorte de Idosos de Bambuí. A incidência acumulada em três anos da hipertensão arterial foi de 37.3%. O risco relativo (RR) para a incidência da hipertensão diminuiu 0,92 para cada unidade de colesterol HDL (IC95%: 0,86-0,99), independente de vários potenciais fatores de confusão. Indivíduos com colesterol HDL no tercil superior ( $\geq 55\text{mg/dL}$ ) apresentaram metade do risco de hipertensão que aqueles no tercil inferior (RR = 0,54; IC95%: 0,33-0,90). Os outros parâmetros lipídicos não apresentaram efeitos estatisticamente significantes sobre o evento. Valores mais altos de colesterol HDL apresentaram efeito protetor para o desenvolvimento da hipertensão em idosos.*

*Dislipidemias; Hipertensão; Idoso; Estudos de Coortes*

## Contributors

M. P. D. Freitas contributed to the conception and design, analysis and interpretation of the data, drafting the article, and final approval of the version to be published. A. I. Loyola Filho collaborated on the analysis and interpretation of the data; revision of the article; and final approval of the version to be published. M. F. Lima-Costa contributed to the conception and design, acquisition of data, analysis and interpretation of the data, revision of the article, and final approval of the version to be published.

## Conflicting interests

None declared.

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