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Inflammation, Oxidation, Caloric Expenditure and Cognitive Impairment in Brazilian Elderly Assisted at Primary Care

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Abstract: Cognitive impairment (CI) has a multifactorial etiology. Some studies have suggested that inflammatory, oxidative and antioxidant status and physical activity are associated with CI. However, the evidence on this subject is still controversial. The goal of this study was to verify the association of caloric expenditure by physical activity, oxidative, antioxidant power and inflammatory biomarkers with CI in older adults. We performed a cross-sectional study of 424 elderly (224 with normal cognitive function and 200 with CI) patients from the Family Health Strategy in Porto Alegre, Rio Grande do Sul, Brazil. The variables investigated were sociodemographic, biochemical, inflammatory (hs-CRP, IL-6), oxidative (TBARS, AOPP), antioxidant power (FRAP) biomarkers, energy expenditure, and cognitive function. The instruments used were the Minnesota Leisure Time Physical Activity Questionnaire + Compendium of Physical Activities, classification of energy costs of human physical activities (for physical activity evaluation and measurement of energy expenditure in METs), and a battery of neuropsychiatric instruments (for cognitive ability assessment). We found statistically significant differences only with respect to HDL-c and age (higher averages in the CI group; $P<0.05$). We observed no differences between the groups with respect to biochemical, inflammatory, oxidative and FRAP biomarkers or caloric expenditure. Logistic regression showed that HDL-c (OR=1.02 [IC=95%; 1.01-1.04]; $P=0.011$), and age (OR=1.05 [IC=95%; 1.02–1.08]; $P=0.004$) are independent factors associated with CI. Our results suggest that the biochemical (except HDL-c), inflammatory, oxidative, and FRAP biomarkers investigated and caloric expenditure are not associated with CI in the elderly assisted at primary care.

Keywords: Aging, antioxidant, caloric expenditure, cognitive impairment, inflammation, oxidation.

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1. INTRODUCTION

One of the conditions most frequently associated with aging is cognitive impairment (CI). During this process, some cognitive functions, for example explicit and working memory, attention and executive function, are more negatively affected than others [1].

The literature has highlighted many factors associated with CI. These include age, low educational level, poor cognitive reserve, family history of the condition, cardiovascular risk factors, genetic composition, chronic disease (diabetes, depression; Parkinson's) and lifestyle (smoking, alcohol, diet, sedentarism, leisure, availability of social networks, and other factors). A number of studies have demonstrated that physical activity is beneficial to the human organism and that it helps preserve good biological, psychological, emotional/affective and cognitive functioning [2]. Low levels of physical activity associated with modern sedentary lifestyles have been implicated in the etiology of dementia and mild cognitive impairment [3].

Some recent studies have suggested that CI may have as part of its etiological basis oxidative stress and inflammation, two mechanisms that are narrowly correlated with each other [2]. Many studies show that high levels of high-sensitivity C-reactive protein (hs-CRP), IL-6 and reactive oxygen species (ROS) are associated with the occurrence of cerebrovascular lesions (ischemia), which can consequently lead to cognitive decline and dementia [4-6]. Other studies

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have suggested that caloric expenditure resulting from physical activity and antioxidant status can act as effective mechanisms to modulate the inflammatory response and oxidative stress, thereby attenuating the effects of aging on cognitive function and preventing dementia [7-9].

In this regard, older adults with significant CI have a higher risk of developing dementia [7, 10]. This fact suggests relevant questions concerning which factors in addition to the classical risk factors that are associated with CI represent protection against or increase the risk of developing this impairment. To date, no studies have verified the association among caloric expenditure by physical activity, markers of oxidative and antioxidant power and inflammatory and CI in older adults. In this context lies the importance of the present article.

2. MATERIALS AND METHOD

2.1. Study Design

A cross-sectional study was conducted involving volunteer older adults of the Multidimensional Study of the Elderly in the Family Health Strategy in Porto Alegre, Brazil (EMI-SUS) [11]. The participants were users of the Family Health Strategy (FHS) of Porto Alegre, Brazil, which provides medical care to the population. Our study included 424 patients (152 men and 272 women) who participated in data collection during the period March to December 2012. The research was approved by the Research and Ethics Committee of PUCRS (protocol 10/04967), and all participants signed the informed consent form. The criteria for inclusion were: 60 years of age or older, being an older adult registered in the FHS, and having participated in psychiatric, neurological and psychological assessments as well a physical activity evaluation. Individuals with depression and/or dementia were excluded from the study. Diagnosis of depression was based on the Geriatric Depression Scale (GDS) [12] and antidepressant use. Diagnosis of dementia was based on the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [13]. All the research subjects were seen by a neurologist, a psychiatrist, a psychologist and a geriatrician to closely observe a possible diagnosis of dementia.

2.2. Variables Analyzed

The following variables were evaluated: sex, age, cognitive function, physical activity, biochemical and oxidative stress [advanced oxidation protein products (AOPP)], ferric reducing ability of plasma (FRAP), thiobarbituric acid-reactive substances (TBARS) and inflammatory biomarkers (IL-6 and hs-CRP.

Cognitive impairment was determined based on the outcome of a neuropsychological battery consisting of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [14, 15] and the Mini–mental State Examination (MMSE) [16, 17]. The CERAD includes tests of verbal fluency, Boston's naming test (brief version), memorization of a list of words, delayed recall of a list of words, recognition of a word list, constructive praxis and evocation of praxis [14, 15].

Physical activity was evaluated using the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ), which was adapted and validated for the Portuguese language [18, 19]. Values corresponding to the METs (metabolic equivalent) for each activity according to the Minnesota questionnaire were extracted from the Physical Activities Compendium proposed by Ainsworth [20]. For classification of the level of physical activity, values expressed in METs were converted to Kcal/week using the equation IAM = Σ (I xM x F x T), where IAM corresponds to the individual's energetic expenditure during the last two weeks, I represents the intensity of each activity in METs, M is the number of months/year over which the activity was performed, F is the average number of times in which the activity was performed in a month and T is the average duration of the activity per occasion. Values in kilocalories were obtained by multiplying I by the constant 0.0175 x the weight of the individual in Kg [19].

2.3. Biochemical, Oxidative and Inflammatory Determinations

Blood samples were collected from individuals after 12-h overnight fasting by venous puncture into gray and red top Vacutainer tubes (BD Diagnostics, Plymouth, UK) without anticoagulant. The specimens were centrifuged within 1 h of collection for 15 min at 2500 X g, and aliquots of the serum samples were stored at 20 C. Biochemical determinations of total cholesterol, HDL-c, LDL-c, triglycerides and fasting glucose in venous blood samples were performed. The biochemical assays were performed by spectrophotometry in a semi-automated biochemical analyzer (TP Analyzer Basic – Thermo Plate). The biochemical tests were carried out with Labtest® kits (Vista Alegre, Minas Gerais, Brazil): total cholesterol – enzymatic system by endpoint reaction; cholesterol HDL – system of selective precipitation of low and very low density (LDL and VLDL) lipoproteins by endpoint reaction; glucose – enzymatic system by endpoint reaction; and triglycerides – enzymatic system by endpoint reaction. For individuals with TG < 400 mg/dL, LDL was determined by the Friedewald equation [21].

Plasma advanced oxidation protein product (AOPP) levels were measured by Cobas Mira® (Roche Diagnostics, Basel, Switzerland) according to the method described by Hanasand *et al.* [22]. The results were calculated based on a standard curve in mol/L and are given as the equivalent of chloramine. The ferric reducing ability of plasma (FRAP) was measured in the Cobas Mira® according to Benzie and Strain [23]. TBARS were measured using the spectrophotometric method described by Janero [24]. IL-6 and hs-CRP was measured using a chemoluminescence immunoassay method (IMMULITE®/IMMULITE® 1000 IL-6 and hs-CPR) according to the manufacturer's instructions.

2.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17.0 [25]. The data were statistically analyzed by comparison of averages: Student's T test for quantitative variables and the chi-square test (Pearson) for categorical variables. Logistic regression was used to evaluate the association between cogni-

tive impairment (dependent variable) and the independent variables age, marital status, income, total caloric expenditure, total time spent in physical activities, glucose, total cholesterol, LDL, HDL, triglycerides, CRP-us, IL-6, AOPP, FRAP and TBARS. The variables that presented statistical relevance ($P \leq 0.20$) in the univariate and bivariate analysis were submitted to multiple logistic regression model with a stepwise automatic extraction method [26]. Statistical analyses were performed in which all *P* values were two-tailed; $P<0.05$ was considered statistically significant.

3. RESULTS

The sample consisted of 424 older adults (152 men and 272 women), of whom 200 were diagnosed with CI and 224 were without CI. The mean age was 67.4±5.7 years for the normal cognitive group and 69.4±7.0 years the CI group ($P=0.002$). The sociodemographic characteristics of the sample are presented in (Table **1**).

Statistically significant difference was found in relation to age ($P=0.002$). It was observed that individuals with CI were older than individuals without CI. When comparing the biochemical, inflammatory and oxidative markers between the groups, a statistically significant difference was found only in relation to HDL-c levels ($P=0.006$). Older adults with CI presented higher HDL levels than individuals in the group without cognitive impairment, as is shown in (Table **2**).

With respect to caloric expenditure and time spent in light, moderate and vigorous physical activity, there were no statistically significant differences between the groups with and without CI, as demonstrated in (Table **3**).

The final model obtained based on multiple logistic regression is presented in (Table **4**). The results show that age and HDL-c are independent factors associated with CI, having OR=1.05 (IC=95%; 1.02–1.08, $P=0.004$) and OR=1.02 (IC=95%; 1.01–1.04; $P=0.011$), respectively (Table **4**).

DISCUSSION

Epidemiologic evidence suggests that physical activity level, caloric expenditure, and inflammatory and redox metabolism biomarkers are factors associated with the incidence of dementias such as Alzheimer's disease or vascular dementia [2, 27-29]. On the other hand, information regarding the association of these risk factors with CI is scarce or inconsistent. Rare studies indicate an association between inflammatory and oxidative markers, level of physical activity and CI in elders [30]. However, most research on Alzheimer's disease focuses on already established disease. It is also important to consider that most studies have been performed with individuals with cognitive decline and not with individuals with CI as in the present study. In this sense, the present study is the first to describe the lack of association between inflammatory (hs-CRP and IL-6) and oxidative (TBARS and AOPP) markers, antioxidant power (FRAP) and caloric expenditure in older adults with and without CI. Corroborating our findings, Wichmann *et al*. also found no significant association between IL-6 levels and CI. However, that study found that patients not using statins showed the highest values of IL-6 and that these patients had a 3-fold higher risk of having some deficit in cognition than subjects with lower mean IL-6 levels [31]. On the other hand, in a study involving 377 adults with CI and 66 controls, it was found that individuals with CI had significantly higher mean CRP levels than those in the control group. Inflammation may contribute to cognitive impairment due to a series of inflammatory reactions leading to neurodegeneration [32]. Studies on cognitive decline, Alzheimer's disease and inflammation are plentiful in the literature. For example, the results of a cohort study [33] in which the concentrations of hs-CRP and IL-6 were monitored over a period of 12 months in individuals with amnestic cognitive decline corroborate our findings. These authors found an increase in the concentrations of hs-CRP, but not of IL-6, during the 12- month period. However, no significant association with cognition was observed, suggesting the lack of a relationship between systemic inflammation and amnestic cognitive decline. In our study (cross-sectional), we did not classify cognitive decline into amnestic and non-amnestic subtypes; instead, our study only specified whether the participants presented CI based on their performance on neuropsychological tests. Moreover, we also found no association between hs-CRP and IL-6 levels and CI. Perhaps the chronic low-grade inflammation as found in metabolic disorders, for example in metabolic syndrome [34], do not have such a profound impact on cognitive function in older In another study, Yarchoan *et al*. obtained results similar to ours regarding the association of CRP with cognitive decline diagnosis and progression [35]. The authors measured and followed for three years the levels of CRP in elders with Alzheimer's disease, elders with mild cognitive decline and in normal older adults. The results showed that even after adjustment for sex, age and educational level, the individuals with Alzheimer's had significantly lower levels of CRP than other individuals. However, significant association between plasma CRP changes with time and cognitive decline was not found [35]. A biologically plausible explanation for our results would be that specifically in the case of CI, the inflammatory process must be site-specific to cause neurodegeneration, despite the fact that peripheral inflammation enhances neuroinflammation via the hematoencephalic barrier [36]. This may be the reason many studies find an association of inflammatory markers (CRP, interleukins and tumor necrosis factor) with dementia, both Alzheimer's and vascular types, but not with cognitive decline or CI [35, 37, 38]. That leads us to think that because of the endothelial dysfunction of the hematoencephalic barrier, the inflammatory process becomes more harmful to neurons and glial cells, as well as to synaptic connections, with the possibility of initiating dementia. Nevertheless, studies involving other methodological frameworks (longitudinal) and neuroimaging biomarkers are most appropriate to reveal the impact of these factors in the development of CI and to determine whether hs-CPR-us and IL-6 levels can really be considered risk factors for CI in elders.

Our results also did not demonstrate an association between levels of oxidative metabolism markers (TBARS and AOPP) or oxidant power (FRAP) and CI. Rare studies have reported the association between oxidative markers and CI in older adults [39]. Most studies using these biomarkers have been conducted in experimental models or in elders with Alzheimer's or vascular dementia [5, 40].

Table 1. Comparison of sociodemographic variables between older individuals with and without cognitive impairment.

Variable	Total sample N (%)	CI Frequency %	P
Sex			
Male	152 (35.8)	45.4	0.584
Female	272 (64.2)	48.2	
Marital status			
Single	65 (15.5)	47.7	0.079
Married	158 (37.7)	40.5	
Separated	75 (17.9)	48.0	
Widowed	121 (28.9)	56.2	
Educational level			
Illiterate	97 (22.9)	41.2	0.878
Incomplete middle school	264 (62.3)	51.9	
Complete middle school	63 (14.9)	36.5	
Income			
No income	32 (8.1)	53.1	0.052
Up to1 m.w.	205 (51.6)	51.7	
Up to 2 m.w.	133 (33.5)	42.9	
>2 m.w.	27 (6.8)	37.0	

CI: cognitive impairment; *P*: x^2 Pearson test; m.w.: minimal wage.

Table 2. Comparison of biochemical, inflammatory, oxidative and antioxidant power markers between older individuals with normal cognitive function and individuals with cognitive impairment.

Variable	Cognition				*P*
	Normal		CI		
	N	mean±SD	N	mean±SD	
Age (years)	208	67.40±5.71	186	69.39±7.03	0.002
Glucose (mg/dL)	208	120.07±44.08	186	119.62±54.96	0.929
Cholesterol (mg/dL)	208	189.51±40.24	186	196.1 ±42.83	0.116
LDL-c (mg/dL)	206	109.4±37.00	184	113.67±39.66	0.272
HDL-c (mg/dL)	208	49.16±12.69	186	52.87±14.14	0.006
Triglycerides (mg/dL)	209	161.4 ±115.05	186	151.27±79.20	0.314
IL-6 (pg/mL)	130	3.50±3.18	121	4.23±5.70	0.206
hs-CRP (mg/dL)	188	0.41±0.66	171	0.54±1.14	0.205
AOPP (µmol/L)	205	107.56±122.83	185	117.62±107.38	0.392
FRAP (µmol/L)	205	973.44±959.20	185	1007.67±1030.91	0.734
TBARS (µmol/ml)	78	1.69±0.51	61	1.68±0.44	0.971

CI: cognitive impairment; IL-6: interleukin-6; hs-CRP: high-sensitivity C-reactive protein; AOPP: advanced products of protein oxidation; FRAP: ferric plasmatic reduction ability; TBARS: thiobarbituric acid reaction. *P*: Student's T test was applied for independent samples.

Table 3. Comparison of caloric expenditure and time spent in physical activity between older individuals with normal cognitive function and individuals with cognitive impairment.

Variable	Cognition		*P*
	Normal (N= 211) mean±SD	CI (N= 187) mean±SD	
Total caloric expenditure (kcal)	5849.14±7878.47	5338.25±7593.80	0.512
Caloric expend. - light act. (kcal)*	3559.55±4059.54	2887.46±3178.87	0.069
Caloric expend. - moderate act. (kcal)†	1572.37±3719.54	1843.27±4951.77	0.535
Caloric expend. - vigorous act. (kcal)‡	717.23±2438.38	607.52±2099.24	0.633
Total time spent in activity (min)	452.08±665.47	518.69±808.60	0.368
Time spent in light act. (min)	151.29±148.02	128.39±128.28	0.102
Time spent in moderate act. (min)	273.19±606.75	356.50±743.01	0.225
Time spent in vigorous act. (min)	27.61±77.31	33.80±124.09	0.546

CI: cognitive impairment. *Caloric expenditure in light intensity activity (Kcal); †Caloric expenditure in moderate intensity activity (Kcal); ‡Caloric expenditure in high intensity activity. *P*: Student's T test was applied for independent samples.

Table 4. Independent factors associated with elders' cognitive impairment based on the multiple logistic regression model.

Variables	B	Wald	Valor-p	OR	CI of 95%
Age	0.047	8.27	0.004	1.05	1.02–1.08
HDL-c	0.020	6.40	0.011	1.02	1.01-1.04
Constant	-4.356	13.41	<0.001	0.08	

OR: Odds ratio.CI: confidence interval.

Berr *et al.* (2000) [41] conducted a cohort study of older adults with normal cognitive performance aiming to verify whether systemic oxidative stress (TBARS) and antioxidant molecule levels are associated with cognitive decline. After monitoring the participants for four years, the results showed that elders with high levels of TBARS presented an OR = 2.25 (IC = 95%) of developing cognitive decline and that elders with low levels of selenium had an OR = 1.58 (IC = 95%), suggesting that increased oxidative stress or antioxidant inefficiency may be a risk factor for cognitive decline. Studies of the association between oxidative stress and CI are still scarce, and studies of the relationship between levels of novel biomarkers such as AOPP and FRAP and CI in older individuals are nonexistent. AOPP is a novel marker of protein oxidation and inflammation and has been associated with a number of diseases [22, 42, 43]. On the other hand, FRAP is a measurement of ferric reduction ability or plasma antioxidant power. The literature also contains reports of the association between FRAP and specific diseases. Devore *et al*. conducted a study with the objective of evaluating the total antioxidant capacity of the diet on ferric antioxidant reduction power (FRAP) in relation to cognition in older women. The authors found a weak association between the antioxidant capacity of the diet (excluding supplements) and cognitive function. However, they did not find an association between FRAP and cognition when the data were adjusted to multiple factors of confusion [44]. The usual diet of the older adults in our study was not evaluated; thus, diet might have influenced our findings.

Our study also did not show significant differences in caloric expenditure and time spent in physical activity in groups with and without CI. With aging, there is a tendency toward loss of functionality and independence and to reduction in physical activities frequency, which consequently reduce time spent in physical activity and caloric expenditure. It is fundamental to emphasize that health benefits from caloric expenditure, provided by physical activity and recommended by the American College of Sports Medicine, the Sports Medicine Brazilian Society, the Task Force on Preventive Services and the American Heart Association, is a minimum of 2.000 Kcal weekly [45, 46]. Older adults from our sample had, on average, caloric expenditure higher than recommended, which may explain the findings regarding no association with redox and inflammatory metabolism markers, since physical activity has strong modulatory effects in these processes. Thus, physical exercise might be able to control the production of free radicals and inflammatory cytokines or mitigate the harmful effects of oxidative stress and inflammation in the body as a whole.

Logistic regression showed that age and level of HDL-c are predictors of CI in the investigated sample. Age is a risk factor that is associated with the development of cognitive decline and dementia, mainly Alzheimer's [47, 48]. Our results found significant differences in age and levels of HDL-c in older adults with and without CI. These findings are corroborated by the results of other studies [49, 50]. Regarding HDL-c, the results presented in this study show a significant association with CI. Older adults with CI have higher averages of HDL-c than older adults without CI. However, these findings are inconsistent with the results of other studies that indicate that low levels of HDL-c are associated with various comorbidities such as coronary artery disease, metabolic syndrome, cerebrovascular disease and AD [51]. Low levels of HDL, along with other risk factors such as obesity, high levels of triglycerides, hypertension and high fasting glucose, predispose the organism to metabolic syndrome, which is an important cerebrovascular risk factor associated with a decrease in cerebral blood flow. Recent studies suggest a relationship between cognitive decline and reduction of blood flow in various regions, indicating cerebral hypoperfusion as a possible cause of cognitive decline [52, 53]. Nevertheless, our data did not corroborate what many studies suggest, which is a significant association of dyslipidemic conditions, high levels of cholesterol LDL and low levels of cholesterol HDL with the occurrence of cognitive decline and neurodegenerative diseases, mainly Alzheimer's disease. However, it is important to emphasize that our study did not investigate the cognitive decline, but CI. The latter findings suggest that the increase of adiposity alters the function of the hematoencephalic barrier and that changes in the HDL/LDL ratio may facilitate the entry of inflammatory lipids into the blood, leading to CI [54, 55]. However, it is important to consider that the HDL measured in the current study is the ester cholesterol carried by high density lipoprotein particles (HDL). HDL is an extremely heterogeneous mixture of lipoprotein particles, and this heterogeneity is probably caused by continuous exchanges between its various subfractions or subpopulations, exchanges that are influenced by several plasma factors [56]. Furthermore, HDL particles carry almost a hundred different proteins and enzymes, making them a potential target for oxidizing agents. The literature has also shown that HDL particles play an important role in preventing the oxidation of LDL-c and as an anti-inflammatory molecule [57]. Perhaps this is why our findings showed no association between inflammatory and oxidative markers and CI.

The present study has some limitations. The first one, and perhaps the most import, is related to the study design, defined as a cross-sectional study. These studies provide measurements only from a single moment, being impossible to establish cause-and-effect relationships. The second limitation concerns bias associated with the participants educational and income level. The sample was composed of elderly of very low education and income, which does not allow us to make other comparisons. Low income and educational levels may have adverse implications in various dimensions of people's lives, including self-care, self-perceived health, as well as in mental and intellectual dimensions, which could cause misinterpretation of the results. Furthermore, no information was obtained about usual diet and body composition (adiposity) of the participants; these are factors that may also have a potential influence on the results regarding whether inflammatory markers, oxidative metabolism and antioxidant power are associated with cognition. Finally, the study did not investigate the participants' APOE genotypes, which can also be considered a limitation.

Despite the limitations of our study, it is important to point out that it was the first one to address the energy expenditure issue and show the AOPP, FRAP and inflammatory markers profile in Brazilian older adults with cognitive impairment assisted in primary health care. So far, it has not been reported in the literature another article with this approach. It nevertheless contributes to a better comprehension of the CI etiopathology in older adults with very low income and education. It brings new perspectives to the investigation of novel redox metabolism and inflammatory biomarkers that are allied to genetic, adiposity and neuroimaging variables that might be associated with cognitive impairment.

CONCLUSION

The results of this study suggest that there is no association of inflammatory (hs-CPR and IL-6), oxidative (TBARS and AOPP) and antioxidant power (FRAP) biomarkers and energy expenditure with CI in the investigated sample of elderly assisted at primary care. Additionality, multivariate analysis showed that age and HDL-c are independent factors associated with CI. However, more studies need to be conducted in order to better understand the role of redox metabolism and caloric expenditure associated with CI in the elderly.

LIST OF ABBREVIATIONS

AOPP	=	Advanced oxidation protein products
CERAD	=	Consortium to Establish a Registry for Alzheimer's Disease
CI	=	Cognitive impairment
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EMI-SUS	=	The multidimensional Study of the Elderly in the Family Health Strategy in Porto Alegre, Brazil
FHS	=	Family Health Strategy
FRAP	=	Ferric reducing ability of plasma
hs-CRP	=	High-sensitivity C-reactive protein
IL-6	=	Interleukin 6
MET	=	Metabolic equivalent
MLTPAQ	=	Minnesota Leisure Time Physical Activity Questionnaire
MMSE	=	Mini–Mental State Examination
ROS	=	Reactive oxygen species
TBARS	=	Thiobarbituric acid reactive substances

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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