Body Mass Index as a predictor of multimorbidity in the Brazilian population

Índice de Massa Corporal como preditor de multimorbidade na população brasileira

Marina Christofoletti¹
Anne Ribeiro Streb¹
Giovani Firpo Del Duca¹

Abstract – Overweight is a health risk indicator, but little is known about its influence on the chronic non-communicable diseases (NCD) multimorbidity. The aim of this study was to identify the predictive values and sociodemographic factors associated with Body Mass Index (BMI) as a determinant of the occurrence of NCD multimorbidity in Brazilian men and women. Data from the “Surveillance of risk and protection factors for chronic diseases by telephone survey” - 2013 national survey were used. The population was composed of ≥18 year-old individuals and those living in house with a fixed telephone line in the 27 Brazilian’s capitals. The outcome variables were BMI and its respective predictive value for the occurrence of multimorbidity (≥2 NCDs). The exposure was age, marital status and educational level. Inferential statistics included the construction of Receiver Operating Characteristic curves (cutoff point defined by sensitivity [Se] and specificity [Sp]) and the association by Poisson Regression, stratified by sex. The values with the best predictive capacity for multimorbidity were 26.7 kg/m² (Se = 60.9%, Sp = 60.2%) for men and 25.7 kg/m² (Se = 61.8%, Sp = 61.1%) for women. The predictive multimorbidity value followed the progress of age groups up to 55 to 64 years for both groups. Women with higher educational level showed an inverse association for the presence of the outcome. BMI can be considered a predictor of the occurrence of multimorbidity, and sociodemographic profile associated with this predictive value was advancement age and inversely associated with educational level in women.

Key words: Chronic disease; Cross-sectional studies; Epidemiologic studies; Nutritional status; ROC curve.

Resumo – O excesso de peso corporal é um indicador de risco para a saúde, porém pouco se sabe sobre sua influência diante da multimorbidade de doenças crônicas não transmissíveis (DCNT). Objetivou-se identificar os valores preditivos e os fatores sociodemográficos associados ao Índice de Massa Corporal (IMC) como determinante da ocorrência de multimorbidade de DCNT em homens e mulheres brasileiras. Utilizaram-se dados do inquérito “Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico” - 2013. A população foi composta por indivíduos com ≥18 anos e residentes em domicílios com linha telefônica fixa nas 27 capitais brasileiras. As variáveis de desfecho foram o IMC e seu valor preditivo para a ocorrência de multimorbidade (≥2 DCNT). As exposições foram idade, estado civil e escolaridade. A estatística inferencial contou com a construção de curvas Receiver Operating Characteristic (ponto de corte definido pelo valor de sensibilidade [S] e especificidade [E]) e a associação por meio da Regressão de Poisson, estratificadas por sexo. Os pontos de corte com melhor capacidade preditiva de multimorbidade de DCNT foram de 26,7kg/m² para homens (S=60,9%; E=60,2%) e 25,7kg/ m² para mulheres (S=61,8%; E=61,1%). O valor preditivo da multimorbidade acompanhou o avanço das faixas etárias até 55 a 64 anos para ambos os grupos. Mulheres mais escolarizadas apresentaram tendência de proteção para presença do desfecho. O IMC pode ser considerado predutor da multimorbidade, e o perfil sociodemográfico que esteve associado ao valor preditivo de multimorbidade foi o avanço da idade e inversamente associado à escolaridade em mulheres.

Palavras-chave: Curva ROC; Doença crônica; Estado nutricional; Estudos epidemiológicos; Estudos transversais.
INTRODUCTION

The high prevalence and mortality caused by Chronic Noncommunicable Diseases (NCD) is considered a public health problem, affecting populations in different socioeconomic conditions. The deleterious individual effects of these chronic diseases result in survival with considerable negative effects on quality and life expectancy, such as the existence of concomitant new diagnoses. There are non-modifiable and modifiable risk factors, among them obesity, which is shown to be an independent factor for cardiovascular diseases. It is also associated with the simultaneity of metabolic, psychological, hormonal and joint diseases. Therefore, this condition provides a favorable scenario for the aggregation of other NCD due to the detrimental effects on health considering the chronic accumulation of visceral and subcutaneous adipose tissue. Previous studies have shown that increased Body Mass Index (BMI) is directly related to cardiovascular and endocrine diseases, such as Type 2 Diabetes Mellitus, dyslipidemia and systemic blood hypertension.

Excess weight may be accompanied by other diagnoses, which in turn can trigger multimorbidities (presence of two or more diseases simultaneously in the same individual). Multimorbidity has similar characteristics with NCD in general, but there is a greater magnitude of deleterious effects due to the accumulation of chronic diseases, with the individual impact of each disease. Such health status deserves attention both in adults and in the older adults, mainly due to the financial impacts generated by the increase in the continuous use of medications, number of medical consultations and demand for health services.

When considering health as a dynamic state, susceptible to different simultaneous diagnoses, an alternative is necessary for the diagnosis and characterization of population at risk for multimorbidities, especially in the primary health care. In this sense, nutritional status appears as an interesting alternative for the prediction of such outcome because it is an indicator of simple measurement and low cost. However, few works on the multimorbidity issue have been conducted in Brazil, a nation in rapid epidemiological transition. In addition, the identification of the sociodemographic profile contributes to the definition of preventive measures in public health directed to the population subgroups most exposed to health risk outcomes. Therefore, the aim of the present study was to identify the predictive values and sociodemographic factors associated with Body Mass Index (BMI) as a determinant of the occurrence of NCD multimorbidity in Brazilian men and women.

METHODOLOGICAL PROCEDURES

The present study has cross-sectional design and is derived from the “Vigilance of risk factors and protection for chronic diseases by telephone inquiry” system, also known as VIGITEL, under the supervision of the
Health Surveillance Secretariat, an organ from the Ministry of Health. Data were collected between February and December of 2013 and the report was published in 2014. The target population consisted of Brazilian adults aged ≥18 years living in capitals of the 27 Brazilian federative units, who had access to a phone line in their residence.

The probabilistic sampling process was carried out in three stages. In the first, the selection of telephone lines was carried out using a systematic draw of 5,000 lines, stratified by Zip Code. Telephone lines were divided into sub samples of 200 lines each, reproducing the same proportion of lines by region of the city or area code. The second stage consisted in identifying the eligible lines, occurring at the same time as the interviews, totaling 74,005 lines. Finally, in the third stage, participants were randomly selected for the interview, all adults (≥ 18 years) living in the contacted house13. The estimates produced were adjusted to the Brazilian adult population, using a post-stratification weight that considered sex (female and male), age group (18-24, 25-34, 35-44, 45-54, 55-64 and ≥65 years) and educational level (incomplete or incomplete elementary school, complete or incomplete high school and complete or incomplete higher education). The post-stratification weight of each individual in the sample was calculated by the rake method13.

Data collection took place through a telephone interview with simultaneous computer resources. Further details on the sampling process and data collection are available in the official VIGITEL report13.

As a result of the present study, a multimorbidity variable was created, defined as the presence of ≥2 combined NCD (diabetes, dyslipidemia and blood hypertension). NCD were defined by self-report based on the questions: “Has any doctor ever told you that you have high blood pressure?”; “Has any doctor ever told you that you have diabetes?”; “Has any doctor ever told you that you have high cholesterol or triglycerides?” BMI was used as the main exposure variable. This has been collected by weight information (“Do you know your weight (even if it is an approximate value?)”) and height (“Do you know your height?). Statistical treatment was carried out, in which socio-demographic variables of age, sex, educational level and ethnicity were taken into account for the data imputation in the BMI variable, due to sample losses (8.8%). Exposure variables were sex (male and female), age (categorized from 18 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64 and ≥65 years), marital status (with partner and without partner) and educational level (categorized as ≤8 years, 9-11 years and ≥12 years).

Initially, descriptive analysis was performed, with the presentation of absolute and relative frequencies, in addition to 95% confidence intervals (95% CI). For the inferential analysis, the Receiver Operating Characteristic (ROC) curves were applied to sample stratified by sex, established by the positioning of sensitivity (Se) on the y axis as a function of [1 – specificity (Sp)] the “x” axis14. Sensitivity reports the percentage of affirmatives to the outcome and was correctly diagnosed by means of the indicator (true-positive), while specificity describes the percentage of individuals who did not present the outcome and were correctly diagnosed by means of the
indicator (true-negative)\(^3\). The values in the area of the ROC curve, which represent the specificity and sensitivity pairs with all possible combinations for the determination of a cutoff point, in which by expressing a bisector variable, was determined by the value of 0.50. To consider the presence of a cutoff point, the value of the area under the ROC curve was adopted, in which values above 0.50 show the discriminatory power of BMI for the occurrence of NCD multimorbidity. Following the identification of the discriminatory power, the predictive BMI value for the presence of NCD multimorbidity was extracted by the method that adopts the maximum specificity and sensitivity values. The 95% CI was also considered a determinant of predictive capacity, and for BMI to be considered a significant predictor of NCD multimorbidity, the lowest CI limit (Li-IC) should be \(\geq 0.50\)^17. With the presentation of the discriminant BMI value defined by the ROC curve, which predicts the presence of multimorbidity, it was dichotomized as existing risk and non-existent risk for multimorbidity.

Aiming at analyzing associations of this established cutoff point with independent variables, the Poisson regression was applied with adjusted analyses, maintaining stratification by sex. The hierarchical model of analysis included in the first level exposures of age and marital status, and in the second level, the educational level variable was included. In the selection of variables, the backward selection strategy was used, considering \(p \leq 0.20\) for permanence in the model. Results with \(p\) values \(\leq 0.05\) were considered statistically significant. The software used was Stata, version 14.0 (Stata Corporation, College Station, USA). The command used to consider the sample weight was svy.

The free and informed consent procedure was performed at the time of the interview, and in a verbal manner, considering that the entire collection process was carried out in a single moment during the telephone interview. Approval of the VIGITEL project was obtained by the National Committee for Ethics in Research with Human Beings of the Ministry of Health (process number 355.590).

**RESULTS**

In total, 52,929 interviews were completed, representing response rate of 71.5%. The sample had higher proportion of women (53.9%), aged 25–34 years (25.3%), with no partner (50.6%) and with educational level of 9–11 years (37.3%). The most frequent diagnosis in interviewees was systemic blood hypertension (24.1%), followed by dyslipidemia (20.3%) and diabetes (6.9%). Regarding multimorbidity, 16.4% of adults presented this condition.

The area under the ROC curve in men presented value of 0.65. In this way, BMI seems to provide information on the presence of multimorbidity in this sample. The value indicated to discriminate a cutoff point for the presence of multimorbidity in Brazilian adult males was 60.91% for sensitivity and 60.23% for specificity (Table 1), respectively for BMI of 26.67 kg/m\(^2\) (Figure 1).
The area under the ROC curve value for women was 0.65. Similar to men, the curve of women could be considered with discriminatory power because it is higher than 0.5. The sensitivity percentage was 61.84% and specificity percentage was 61.12% (Table 1), which allowed identifying the cutoff point of the BMI variable that could discriminate the presence of multimorbidity in Brazilian women, with value of 25.76 kg / m² (Figure 2).

Table 1. Information extracted from the ROC curve referring to discriminatory BMI values for the presence of multimorbidity in Brazilian adults. Brazil, 2013 (n = 20,276 men and 32,653 women).

<table>
<thead>
<tr>
<th>Sample</th>
<th>BMI (kg/m²)</th>
<th>Area under the ROC curve</th>
<th>95% CI of area</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>26.67</td>
<td>0.65*</td>
<td>(63.82;65.15)</td>
<td>60.91</td>
<td>60.23</td>
</tr>
<tr>
<td>Women</td>
<td>25.76</td>
<td>0.65*</td>
<td>(64.86;65.94)</td>
<td>61.84</td>
<td>61.12</td>
</tr>
</tbody>
</table>

Note. BMI (Body Mass Index) ROC (Receiver Operating Characteristic); 95% CI (95% Confidence Interval). * (Li-IC ≥ 0.50).
The prevalence ratios resulting from the association between the BMI cutoff point indicated by the ROC curve and sociodemographic variables presented in Tables 2 and 3 allow identifying the sociodemographic profile of those multimorbidity due to the value equal to or higher than the predictive value found. In both men and women, age and marital status were associated with predictive value. In women, educational level presented an inverse association.

Table 2. Association between BMI cutoff point for multimorbidity and sociodemographic variables in Brazilian adult males, Brazil, 2013 (n = 19,489).

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI (26.67 Kg/m²)</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% PR (95% CI)</td>
<td>p</td>
<td>% PR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤0.001*</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>18 to 24</td>
<td>18.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25 to 34</td>
<td>27.3</td>
<td>2.25 (1.85; 2.74)</td>
<td>1.96 (1.60; 2.40)</td>
</tr>
<tr>
<td>35 to 44</td>
<td>19.1</td>
<td>3.18 (2.60; 3.88)</td>
<td>2.45 (1.96; 3.06)</td>
</tr>
<tr>
<td>45 to 54</td>
<td>16.3</td>
<td>3.34 (2.72; 4.09)</td>
<td>2.43 (1.94; 3.04)</td>
</tr>
<tr>
<td>55 to 64</td>
<td>10.4</td>
<td>3.13 (2.52; 3.88)</td>
<td>2.25 (1.76; 2.87)</td>
</tr>
<tr>
<td>≥65</td>
<td>8.9</td>
<td>2.22 (1.79; 2.76)</td>
<td>1.63 (1.28; 2.08)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>≤0.001*</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Without partner</td>
<td>47.7</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>With partner</td>
<td>52.3</td>
<td>2.01 (1.79; 2.26)</td>
<td>1.82 (1.59; 2.08)</td>
</tr>
<tr>
<td>Educational Level (years)</td>
<td>0.229*</td>
<td>0.156*</td>
<td></td>
</tr>
<tr>
<td>0 to 8</td>
<td>39.7</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>9 to 11</td>
<td>37.6</td>
<td>0.83 (0.72; 0.94)</td>
<td>1.00 (0.87; 1.16)</td>
</tr>
<tr>
<td>≥12</td>
<td>22.7</td>
<td>0.95 (0.82; 1.09)</td>
<td>1.12 (0.97; 1.32)</td>
</tr>
</tbody>
</table>

Note: BMI (Body Mass Index); PR (Prevalence Ratio); 95% CI (95% confidence interval); p-value extracted from the Wald test for a Heterogeneity and b Trend; Poisson regression with adjustments by levels, being: Level 1: adjusted for age, marital status; Level 2: educational level.

Table 3. Association between BMI cutoff point for multimorbidity and sociodemographic variables in Brazilian adult women, Brazil, 2013 (n = 28,722).

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI (25.6 Kg/m²)</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% PR (95% CI)</td>
<td>p</td>
<td>% PR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤0.001*</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>18 to 24</td>
<td>14.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25 to 34</td>
<td>23.7</td>
<td>1.90 (1.56; 2.32)</td>
<td>1.71 (1.34; 2.10)</td>
</tr>
<tr>
<td>35 to 44</td>
<td>20.2</td>
<td>3.03 (2.73; 4.00)</td>
<td>2.82 (2.31; 3.44)</td>
</tr>
<tr>
<td>45 to 54</td>
<td>17.5</td>
<td>3.98 (3.28; 4.83)</td>
<td>3.39 (2.77; 4.14)</td>
</tr>
<tr>
<td>55 to 64</td>
<td>12.6</td>
<td>5.37 (4.41; 6.54)</td>
<td>4.71 (3.84; 5.76)</td>
</tr>
<tr>
<td>≥65</td>
<td>11.9</td>
<td>4.31 (3.56; 5.23)</td>
<td>4.00 (3.29; 4.89)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>≤0.001*</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Without partner</td>
<td>53.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>With partner</td>
<td>46.9</td>
<td>1.72 (1.58; 1.89)</td>
<td>1.54 (1.40; 1.69)</td>
</tr>
<tr>
<td>Educational Level (years)</td>
<td>≤0.001*</td>
<td>≤0.001*</td>
<td></td>
</tr>
<tr>
<td>0 to 8</td>
<td>38.7</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>9 to 11</td>
<td>36.1</td>
<td>0.58 (0.52; 0.64)</td>
<td>0.79 (0.71; 0.89)</td>
</tr>
<tr>
<td>≥12</td>
<td>25.2</td>
<td>0.43 (0.38; 0.48)</td>
<td>0.60 (0.53; 0.68)</td>
</tr>
</tbody>
</table>

Note: BMI (Body Mass Index); PR (Prevalence Ratio); 95% CI (95% confidence interval); p-value extracted from the Wald test for a Heterogeneity and b Trend; Poisson regression with adjustments by levels, being: Level 1: adjusted for age, marital status; Level 2: educational level.
In men, multimorbidity was more associated with individuals aged 35-44 and 45-54 years, who had approximately twice the multimorbidity prevalence (PR: 2.45 [95% CI: 1.96, 3.06] and PR: 2.43 [95% CI: 1.94, 3.04], respectively by this discriminant value compared to young adults (18-25 years). Those who reported living with their partners presented higher prevalence by the discriminant multimorbidity value (PR: 1.82 [95% CI: 1.59, 2.08]).

In women, multimorbidity was associated with age group of 55-64 years, who had about five times the multimorbidity prevalence (PR: 4.71 [95% CI 3.84, 5.76]) by this discriminant value compared to young adults (18-25 years). Women living with a partner presented higher prevalence by the discriminant multimorbidity value (PR: 1.54 [95% CI: 1.40, 1.69]). Educational level presented a protective factor, indicating that, regardless of age and marital status, there is a tendency according to educational level (PR: 0.79 [95% CI: 0.71, 0.89]; PR: 0.60 [95% CI: 0.53, 0.68]), with the category of 12 years or older associated with lower chance of presenting multimorbidity through this BMI classification.

**DISCUSSION**

The present study found a discriminatory BMI value for the occurrence of NCD multimorbidity; in addition, it showed association of this value with a sociodemographic profile of risk for multimorbidity. The main findings of this study indicated that for values considered to be overweight\textsuperscript{16}, there is exposure to multimorbidity, mainly associated with middle age, presence of partners and, in particular, women with lower educational level.

The nutritional status, evaluated by BMI, allows estimating the characteristics of a population of men and women in different age groups regarding the risk of cardiovascular diseases\textsuperscript{16}. The discriminant values found in the present study indicate a congruence of risk factors\textsuperscript{16}. In this way, preventive measures and care for heart health should begin before reaching the state of obesity, with care able to promote the maintenance of healthy habits throughout life\textsuperscript{17}. The consequences of increased body mass are already sufficient to promote metabolic overload, with increased mortality proportional to the increase in BMI\textsuperscript{17}.

In men, BMI can be considered as a good predictive measure for the presence of multimorbidity, with greater association in middle-aged adults between 35 and 44 and between 45 and 54 years. It is known that NCD have greater impact according to the healthy lifespan of adults aged 30-59 years, but the prevalence increases over time\textsuperscript{18}, which is not consistent with the results found here. The rationale is the measure applied to the adult and elderly population considered in the study, where the classifications of this evidence comprise adults up to 64 years\textsuperscript{16}. In this case, the reduction in the multimorbidity prevalence in the elderly (> 65 years) does not seem to be the reality, considering that there is an increase in the number of diseases in this population\textsuperscript{19}. Thus, BMI is restricted to adults, suggesting, according to Macedo Bueno et al.\textsuperscript{20}, that anthropometric and biochemical
variables are necessary for the NCD diagnosis, in addition to monitoring the general and nutritional health of this population.

In women, there was an association between ages of 25 and 34 years, with those with 55 and 64 years being the most exposed to the predictive multimorbidity value. Associating age group with the initial increase in prevalence, it could be inferred that the Brazilian female population of urban centers has higher fertility rates between 20 and 29 years\textsuperscript{21}, possibly presenting postpartum weight retention, one of the determinants of obesity in women\textsuperscript{22}. Observing those most exposed, there may be the existence of a relationship with menopause, a hormonal event that occurs on average at 50 years in Brazilian women\textsuperscript{23}, which has effects of increasing body fat and NCD diagnosis\textsuperscript{24}. Thus, for the sample of this study, sensitivity and specificity of the BMI measure for adults with multimorbidity was confirmed. As in men, multimorbidity decreased in the elderly (≥65 years), supporting the rationale that the BMI measure is adequate for adults less than 65 years of age of both sexes\textsuperscript{20}.

Marital status, similar for men and women, corroborates the study carried out in Portugal, in which married or widowed participants are more exposed to multimorbidities than those who are single and divorced. In this case, a broader interpretation can be considered, which indicates that lifestyle becomes less healthy after a marital situation change, leading to an increased risk for cardiovascular diseases, reduction of physical activity, changes in eating patterns and sleep quality\textsuperscript{26}.

Especially for women, educational level showed an inverse association for the BMI value found as a multimorbidity predictor. Educational level is considered an important variable of exposure for health indicators, including NCD\textsuperscript{27}, bringing a perspective that health education can exist in the school and academic environment.

Studies that have identified the discriminatory power and cutoff points are common for studies that have health conditions as outcome\textsuperscript{28}. Therefore, since the 1980s, there are discussions on the best method for detecting predictive value, which has advantages and disadvantages, with recent discussions on the validity method (sensitivity and specificity), maximum Youden index\textsuperscript{29} and the bayesian inference\textsuperscript{28}. The main difference between the first and the second is that sensitivity and specificity consider smaller the proportion of false negatives and positives, while the Youden index reflects the result of the smaller sum of proportions of classification errors\textsuperscript{29}. The bayesian inference allows the integration of previous knowledge with the results of the sample being analyzed, with analysis options considering previous evidence of the variable (predictive value found considering estimates of other samples for the definition of the cutoff point)\textsuperscript{29}.

The present study stands out for showing the result that overweight is already predictive of multimorbidity, unlike what is established by the guidelines of risk indicators\textsuperscript{30}, which indicate obesity as a risk factor for chronic non-communicable diseases, separately. With the reference of this predictive value, this study aims to contribute to attention for the preven-
tion of weight gain, which with the indirect anthropometric measurement, presents an opportunity of applicability of information, considering measures of easy measurement and self-knowledge by the population and health servers. Finally, different regions and their different characteristics in national territory were considered. Some limitations are related to the impossibility of extrapolating these findings to cities with population densities and economic indicators different from those of this study. It should be considered that this was a cross-sectional study of measures extracted from self-reports, which may lead to information bias due to educational level and information recall, especially weight and height. Regarding the adopted anthropometric measure, indicators of central obesity could have been used in order to complement the discriminatory power for the existence of NCD multimorbidity. Another point is that, because it is a study that contemplates many aspects of the health of Brazilians, only the most prevalent NCD in the country are considered in the survey, not considering psychological and orthopedic diseases, for example.

It was concluded that BMI is an important tool for epidemiological studies for the early detection of NCD simultaneity. As an easy-to-use measure, future actions in primary health care can use this resource. In addition, the prevention and treatment of multimorbidity is characterized by the knowledge of sociodemographic factors associated with it, which in the population of Brazilian capitals, provide care for middle-aged adults with partners and lower educational level.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical approval
Ethical approval was obtained from the local Human Research Ethics Committee – National Commission for Research Ethics - Department of Health Surveillance (No 355.590), and the protocol was written in accordance with standards set by the Declaration of Helsinki.

Conflict of interest statement
The authors have no conflict of interests to declare.

Author Contributions
Conceived and designed the study: GFD, MC. Analyzed the data: MC. Wrote the paper: MC, ARS. Revised the manuscript: GFD

REFERENCES

CORRESPONDING AUTHOR
Marina Christofoletti
Federal University of Santa Catarina, Department of Physical Education.
Vereador Frederico Veras Street, Florianopolis, Santa Catarina, Brazil.
Zip Code: 88040-230
E-mail: marinachriss@outlook.com