

## Effects of Physical Exercise on Lipid and Inflammatory Profile of Women Using Combined Oral Contraceptive: A Cross-Over Study

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### Abstract

**Background:** The use of combined oral contraceptives (COC) is a risk factor for atherosclerotic disease, and physical exercise can minimize this condition.

**Objective:** To verify if high intensity interval training (HIIT) promotes changes in the lipid and inflammatory profile of women using COC.

**Methods:** Sequential crossover study with women aged 20-30 years, classified as irregularly active by the international physical activity questionnaire (IPAQ), when using COC. A physical-clinical assessment was performed with anthropometric measurements,  $VO_{2max}$ , and analysis of lipid and inflammatory profile. Participants were divided into 2 groups: the initial intervention group (GII), which began practicing HIIT for 2 months, and the posterior intervention group (GIP), which remained inactive for the same period. The GII and GIP would then alternate their conditions. The collected data was divided into: Initial moment (IM), post-exercise moment (PEM) and post-inactivity (PIM). The statistical analyses were performed using the Statistical Package for the Social Sciences, adopting a significance level of  $p < 0.05$ .

**Results:** Twelve women were evaluated. After crossing the GII and GIP data, there was a difference in the C-reactive protein values between the IM of 4 (1.6-6.3 mg/dL) vs. PEM 2 (1.5-5 mg/dL); as well as between the PEM vs. the PIM= 4 (1.5-5.8 mg/dL), with a  $p$ -value = 0.04 in the comparisons. There was no change between the “moments” of the lipid profile, although it was possible to notice a reduction in resting HR and an increase in indirect  $VO_{2max}$ .

**Conclusion:** The HIIT program was able to reduce the inflammatory profile, but it did not alter the lipid profile of irregularly active women using COC.

**Keywords:** Women; Physical Activity; Contraceptives, Oral, Combined; Atherosclerosis; Risk Factors; Lipids; Inflammation; High Intensity Interval Training.

### Introduction

Historical reports state that women started using rudimentary contraceptive methods at least four thousand years ago.<sup>1</sup> Over time, these methods have improved, until between the 1950s and 1960s, the first

oral contraceptives appeared in the United States of America.<sup>2,3</sup> Mostly made up of substances known as ethylinestradiol and progestin, oral contraceptives started to be commercialized worldwide in a short time due to their effectiveness, low cost, and feasibility of use.<sup>3</sup>

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Despite their relevance, it is important to note that oral contraceptives are associated with several side effects, since all blood vessels in the human body have receptors for the hormones estrogen and progesterone. The use of ethyl estradiol and progestin, respectively synthesized based on these endogenous substances, promotes local hyperstimulation and the development of a cascade of consequences.<sup>4</sup>

Among the possible responses to the use of oral contraceptives, it is important to highlight the increase in endothelin, peroxynitro, angiotensin 2, oxidative stress, and insulin resistance.<sup>5,6</sup> In addition, there may be a reduction in the production of nitric oxide, prostacyclin, and changes in hepatocytes.<sup>5-8</sup> All of these new conditions favor thrombolytic, vasoconstrictive, inflammatory, and lipid changes, which, in combination, promote a series of cardiovascular injuries that are determining factors for atherosclerotic disease.<sup>5,9,10</sup>

It is well-known that the inflammatory and lipid profiles are higher in users of combined oral contraceptives (COC),<sup>11,12</sup> especially in those who have lower levels of physical activity.<sup>11</sup> With this in mind, physical exercise has been used to mitigate, or even reverse, these conditions in some populations.<sup>13</sup> However, in our previous studies, there were no clinical trials that verified the cause-effect relationship of physical exercise in the population of women using COC.<sup>11,12,14-16</sup>

Thus, the present study aimed to test the hypothesis that high intensity interval physical exercise promotes changes in the lipid and inflammatory profile of young normolipid women who are irregularly active and using COCs.

## Methods

This is a cross-sectional study, logged in the Brazilian Registry of Clinical Trials (BReCT) under protocol number RBR-4jm343. Participants, aged 20-30 years were evaluated and were nulliparous, with fasting triglycerides  $\leq 150$  mg/dl and a continuous use of oral contraceptives for at least 6 months. In addition to the criteria mentioned above, the participants should be classified as irregularly active by the international physical activity questionnaire (IPAQ).<sup>17</sup>

Those who did insufficient physical activity, with a minimum of 10 continuous minutes during the week, were classified as irregularly active, in addition to not meeting any of the criteria below:

1. Perform 3 or more days of vigorous activity during the week lasting  $\geq 20$  minutes a day;
2. Perform 5 or more days of moderate activity during the week or more than 30 minutes of walking per day;
3. Perform 5 days of any combination of moderate, vigorous activities or walks that reach 600 MET-min/week.

Women with osteomyoarticular changes or pain complaints potentiated by physical exercise, liver dysfunction, pre-diabetes or diabetes, hypo or hyperthyroidism, kidney diseases due to use of anabolic steroids, history of alcoholism, smoking, corticosteroids, hypolipidemics, diuretics or beta-blockers, muscle mass (BMI)  $>30$  kg/m<sup>2</sup>, and polycystic ovary syndrome were excluded.

Throughout the study, the guidelines on research with human beings in the Declaration of Helsinki and Resolution 466/12 of the National Health Council were observed. This study was submitted to and approved by the Research Ethics Committee of Faculdade Nobre de Feira de Santana, logged under protocol number CAAE: 79549517.3.0000.5654. All participants received detailed information on the study objectives, risks, and benefits involved in the procedures, and signed the free and informed consent form.

The sample calculation was performed based on a pilot study consisting of 3 participants, considering an alpha = 0.05 (bidirectional) and a beta = 0.80 and adopting a significant difference of 20% for the variable triglycerides between the analyzed times. Bearing in mind that the laboratory variation coefficient of triglyceride dosage is 5% and that a difference four times greater than expected cancels the bias of this analytical variation coefficient, 12 participants were needed, with 6 allocated to IIG and 6 others allocated to the PIG. The sample calculation was performed using WinPepi, version 11.65.

## Data Collection

To collect general information about the characteristics of the sample, all selected participants underwent a Clinical Physical Assessment (CPA) based on 4 steps, all of which took place at the Fisiocordis Cardiovascular Rehabilitation Clinic, located in the city of Salvador, BA, Brazil, which also provided the space, physical materials, and human resources. The steps were as follows:

**1 = Application of a standard questionnaire:** To screen the sample regarding information relevant to the study protocol at a given time.

**2 = Assessment of vital signs / physical examination:** Composed of measurements of heart rate and systemic blood pressure at rest, total body mass, height, and waist circumference.

To measure the heart rate, a Polar® pulse cardiofrequency meter was used. To measure participants' blood pressure, the recommendations of the Brazilian Society of Hypertension were followed, using a sphygmomanometer and stethoscope from the WelchAllyn® and Littman® brands, respectively.

Height was measured with the help of a professional Sanny® stadiometer with a precision of 0.1 cm, performed with the participants barefoot, with the buttocks and shoulders supported on a vertical back. Total body mass was obtained with a Filizola® digital scale with a maximum capacity of 150 kg, as measured by INMETRO, with its own certificate specifying a margin of error of  $\pm 100$  g. The abdominal circumference was obtained with a metallic and inelastic measuring tape, brand Starrett®, with a measurement definition of 0.1 cm. It was measured in the smallest curvature located between the last rib and the iliac crest without compressing the tissues.<sup>18</sup>

The body mass index (BMI) was calculated with the measures of mass and height, according to the Quetelet equation:  $BMI = \text{mass (kg)} / \text{height}^2 \text{ (m)}$ . The cutoff points adopted were those recommended by the IV Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Department of Atherosclerosis of the Brazilian Society of Cardiology,<sup>19</sup> that is, low weight (BMI <18.5), eutrophy (18.5 < BMI <24.9), overweight (25 < BMI <29.9), and obesity (BMI  $\geq 30$ ).

**3 = Graduation test of indirect maximum oxygen consumption ( $VO_{2max}$ ), by means of the Cooper protocol, performed on the treadmill.**<sup>20</sup> In this test, the participants were initially instructed about all stages of the test and later instructed to perform a warm-up in the form of walking at a speed that represents a self-perceived effort level "easy", regulated by the person evaluated, for 5 minutes on a Movement® treadmill without inclination.

Immediately after the warm-up period, the treadmill was switched off and instantly switched on again. From that moment on, the assessment was actually started, and the participants should walk at their own pace

and regulation for the longest possible distance, being allowed to run, march, and walk. After the 12th minute of assessment, the distance covered was viewed on the treadmill odometer and recorded on the participants' record, ending at that moment, with a subsequent cooling down of the treadmill, with a gradual reduction in speed in 2 minutes until the treadmill speed was reset.

If for any possible reason it was necessary to reset the treadmill speed during the 12 minutes of testing, it should be interrupted and canceled that day, with a new performance after 72 hours. However, in our study, there was no need to interrupt any tests.

**4 = Blood collection to check the lipid and inflammatory profile:** On another previously scheduled day, with at least 72 hours after indirect  $VO_{2max}$ , the participants were sent to a laboratory to perform lipid and inflammatory profile through blood sample analysis. This examination was carried out in the morning period, with 12h fasting, between the fifth and tenth days of the menstrual cycle, considering the smallest hormonal fluctuations, and/or on the 28th day without medication (inactive phase), as recommended by Casazza et al.,<sup>21</sup> so that the menstrual period did not influence the value of the blood variables analyzed in this test.

The tests were carried out at the Clinical Pathology Laboratory (CPL) of the Barra unit in the city of Salvador, BA, Brazil, which provided the space, physical materials, and human resources needed for collections and laboratory analysis. Total cholesterol (TC) values, including Triglycerides, Low density lipoproteins (LDL) cholesterol, High density lipoproteins (HDL) cholesterol, Very low density lipoprotein (VLDL) cholesterol, and high sensitivity C-reactive protein (CRP) were observed so that, according to these values, the lipid and inflammatory profiles of the sample could be traced. The participants were instructed not to change their diet in the week of the test and not to practice any physical effort other than the normal routine, as well as not to drink alcoholic beverages in the 24 hours preceding the test.

The assessment of total cholesterol with HDL cholesterol and triglycerides was carried out by applying the enzymatic method. LDL cholesterol was calculated by the Friedwald equation ( $LDL = TC - HDL - (\text{Triglycerids}/5)$ ),<sup>22</sup> and non-HDL-C cholesterol was calculated by the difference between TC and HDL

cholesterol. High-sensitivity CRP was measured using the turbidimetry method.

### Monitoring Period

Immediately after blood collection, the first six participants were allocated to the initial intervention group (IIG) and the last six to the posterior intervention group (PIG).

At first, only the participants of the IIG entered the high-intensity interval exercise program, which was also performed at the Fisiocordis Cardiovascular Rehabilitation Clinic. Participants of the PIG remained with the same level of physical activities as before the beginning of the study, with a follow-up period of 2 months for each group. A second CPA was then performed after this period, followed by alternating groups in relation to physical exercise and physical inactivity in another 2 months. Finally, a third and last CPA was performed, reaching a total follow-up time of 4 months, as shown in Figure 1.

It is important to clarify that there was no type of intervention or guidance regarding any variable other than physical exercise for both groups. Thus, the participants were managers of their own diet, both during the two months of physical exercise and during the two months of inactivity.

### Intervention Protocol

In the physical exercise session, both at the beginning and at the end, the blood pressure and heart rate data of the participants were collected. If the expected standards for age and level of effort were checked, activities were continued. The protocol consisted of a high intensity interval training done by means of sprints, performed on a treadmill without inclination, with a frequency of 2 times a week and a total period of 2 months, as previously described.

During the exercise sessions, the warm-up phase lasted 5 minutes with an intensity of 60% of the predicted reserve heart rate (PRHR), calculated according to the following equation:  $\{[(220 - \text{age}) - \text{resting HR}] \times 0,6\} + \text{resting HR}$ .<sup>23</sup> For the conditioning phase, the treadmill speed was then increased until 90% of the CRP was reached  $\{[(220 - \text{age}) - \text{resting HR}] \times 0,9\} + \text{resting HR}$ , maintaining this speed for 1 minute, with a subsequent reduction to the heating speed for the next 2 minutes, configuring the active rest. The sprints were alternated with the moments of active rest 10 times, with respective durations of 1 and 2 minutes, with the last 9 speeds of the sprints and active rests being maintained according to the speeds achieved in the first phase of each of these moments. The cool-down phase at the end of the session maintained a speed identical to the warm-up speed,

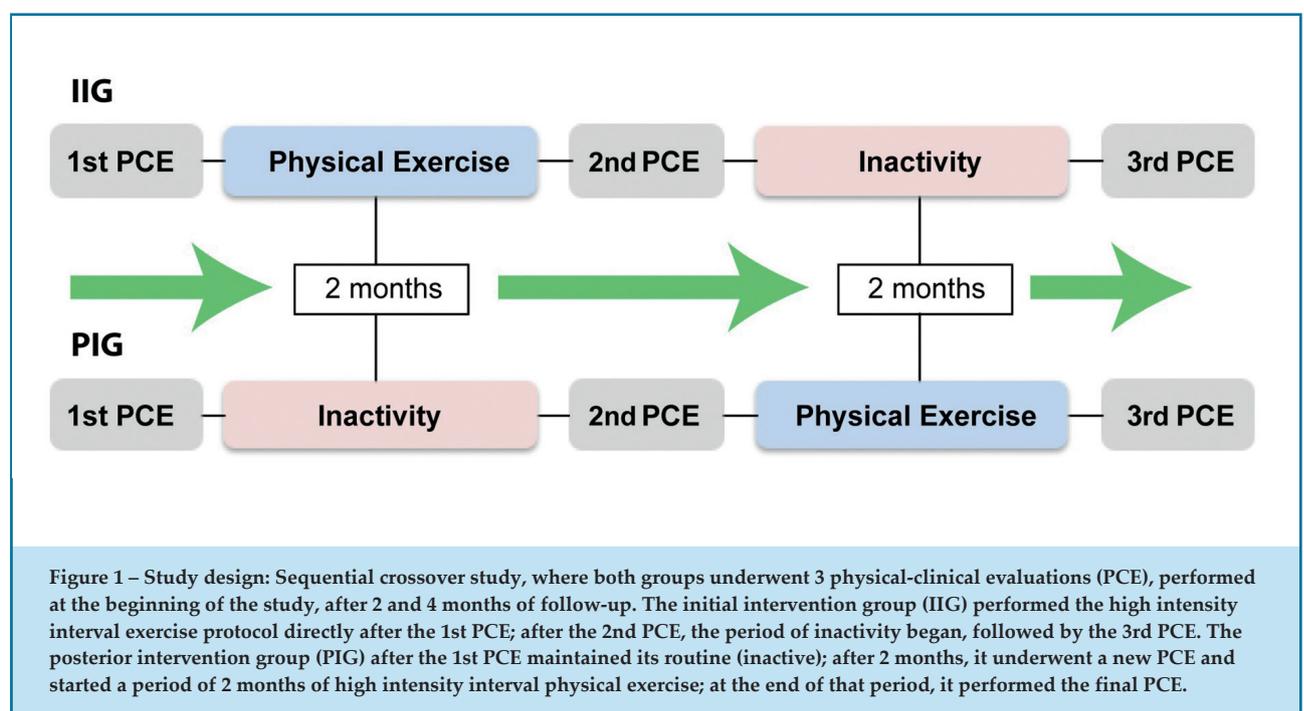


Figure 1 – Study design: Sequential crossover study, where both groups underwent 3 physical-clinical evaluations (PCE), performed at the beginning of the study, after 2 and 4 months of follow-up. The initial intervention group (IIG) performed the high intensity interval exercise protocol directly after the 1st PCE; after the 2nd PCE, the period of inactivity began, followed by the 3rd PCE. The posterior intervention group (PIG) after the 1st PCE maintained its routine (inactive); after 2 months, it underwent a new PCE and started a period of 2 months of high intensity interval physical exercise; at the end of that period, it performed the final PCE.

lasting 2 minutes, until the treadmill was turned off. A summary of this protocol can be seen in Figure 2.

The participants were monitored by the same pulse cardiofrequency meter used during the protocol. Which measured the caloric expenditure of the session, based on BMI, age, maximum expected HR, and average HR during exercise. Each session performed by the same pulse cardiofrequency meter consumed approximately 250kcal, causing a weekly caloric expenditure with the exercise of approximately 500kcal. The interventions had an average duration of 37 minutes.

### Data Analysis

Initially, to verify the data distribution, the symmetry, kurtosis, and Shapiro-Wilk tests were applied, in addition to the visual inspection of the histograms. CRP, which was the only variable with an abnormal distribution, was used as a measure of central tendency and dispersion for the median and interquartile range, respectively, applying the Kruskal Wallis test to measure the comparison between period of activity and inactivity. If the null hypothesis was rejected, the post-hoc DUNN test was used.

For all other variables, the mean and standard deviation was used for data presentation, the Anova test was applied with repeated measures, and Tukey's post-test was used to verify the existence of statistical differences between the moments of exercise and inactivity. All analyses were performed using the SPSS statistical package (Statistical Package for the Social Sciences), version 21.0, adopting a significance level of  $p < 0.05$ .

The results collected from the IIG and PIG groups were distributed in 3 different moments: 1st: initial moment (IM); 2nd: post-exercise moment (PEM), and 3rd: post-inactivity moment (PIM). To assess the data of the "initial moment", the IIG and PIG groups were combined, obtaining the values of central tendency and dispersion resulting from 12 collections.

A cross was made between the data from the PEM and PIM of the IIG and PIG, with the difference that, in the IIG, the data of the PEM were collected 2 months after the beginning of the study, whereas in the PIG these same data could only be collected after four months.

After all data had been collected for crossings, comparisons of the investigated variables were made between the three distinct moments, as follows: IM vs. PEM; PEM vs. PIM, and IM vs. PIM. This crossing

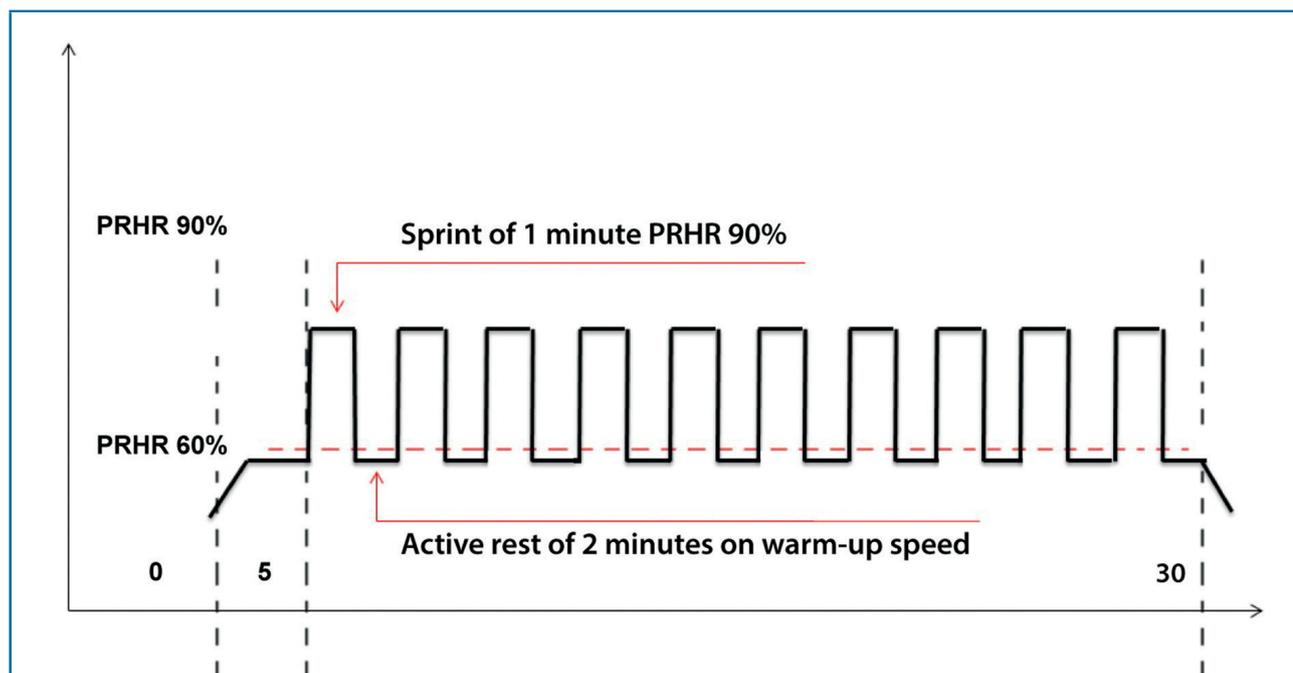


Figure 2 – Representation of high intensity interval training: Training based on predicted reserve heart rate (PRHR). The sprints had a duration of 1 minute and speeds identical to the value reached in the first sprint. Periods of active rest had a duration of 2 minutes and speeds identical to that achieved in the warm-up.

intended for the participants to become their own controls, minimizing bias.

In this study, the predictor variable was high-intensity interval exercise and the outcome variables were triglycerides, HDL, LDL, and CRP. Food and other lifestyle habits, which were not fully controlled, were considered confounding variables.

## Results

Fourteen women were evaluated, one of whom was excluded due to pain complaints in the knee region and the other gave up on continuing the study, withdrawing her informed consent form. Twelve women participated in the research and were divided equally between IIG and the PIG, with 6 in each group, all of whom participated in the exercise and inactivity moments, lasting 2

months each. Table 1 presents the age of the sample and a summary of the oral contraceptives used by the participants. All contraceptives were combined between at least two substances, and 100% of them contained the synthetic estrogen - Ethinyl estradiol in their formulation.

Table 2 shows the comparison of CPE variables in the three moments, with the data already crossed between IIG and PIG. The changes in resting heart rate and  $VO_{2max}$  are highlighted, indirectly obtained through the distance covered in the Cooper protocol.

Figures 3A and 3B show the graphic representation of resting HR and  $VO_{2max}$  in CPE.

As for the inflammatory profile, after crossing the data from IIG and PIG, it was verified that the CRP values changed after the exercise. The CRP had a median and interquartile range of 4 (1.6 - 6.3 mg/dL), respectively, at the initial moment; 2 (1.5 - 5 mg/dL) in the post-exercise

**Table 1 – Age and combined oral contraceptive use for the sample (n = 12).**

Variable	Mean ± Standard Deviation
Age (years)	24 ± 2.5
COC	Percentage of sample in use
<b>Selene</b> Ethinylestradiol 0.035 mg / Cyproterone acetate 2.0 mg	27%
<b>Adoless</b> Ethinylestradiol 0.015 mg / Gestodene 0.060 mg	18%
<b>Tamisa 020</b> Ethinylestradiol 0.020mg / Gestodene 0.075mg	18%
<b>Tamisa 020</b> Ethinylestradiol 0.020mg / Gestodene 0.075mg	18%
<b>Tamisa 030</b> Ethinylestradiol 0.030mg / Gestodene 0.075mg	9%
<b>Level</b> Ethinylestradiol 0.020mg / Levonorgestrel 0.100 mg	9%
<b>Tamisa 030</b> Ethinylestradiol 0.030mg / Gestodene 0.075mg	9%
Active principle	Frequency of the substance in COC
Ethinylestradiol	100%
Gestodene	55%
Cyproterone acetate	27%
Levonorgestrel	18%

**COC - Combined Oral Contraceptives.**

**Table 2 – Physical-clinical evaluation and lipid profile of young women using combined oral contraceptives submitted to high-intensity interval exercise on the treadmill (n = 12)**

Variable	IM	PEM	PIM	P-value
BMI (kg/m <sup>2</sup> )	21 ± 2.6	21 ± 3	21 ± 2.7	0.97
SBP (mmHg)	108 ± 10.8	109 ± 8.7	108 ± 10	0.96
DBP (mmHg)	70 ± 8.0	66 ± 8.5	71 ± 6.1	0.19
Waist (cm)	71 ± 7	72 ± 8	74 ± 6	0.66
Cooper Test (mt)	1337 ± 119	1712 ± 188	1362 ± 199	< 0.01*
TC (mg/dl)	189 ± 19.9	181 ± 26.9	176 ± 19.5	0.37
HDL (mg/dl)	57 ± 11.3	57 ± 12.1	54 ± 9.7	0.67
TG (mg/dl)	100 ± 33.5	107 ± 30.8	111 ± 43.3	0.75
VLDL (mg/dl)	21 ± 4.59	19 ± 3.35	19 ± 3.40	0.60
LDL (mg/dl)	111 ± 22.1	103 ± 25.7	101 ± 17.2	0.53

Values obtained from data from the initial intervention group (IIG) and from the posterior intervention group (PIG), being crossed and expressed as means and standard deviations from the initial moment (IM); post-exercise moment (PEM) and post-inactivity moment (PIM). BMI: body mass index; SBP: systolic blood pressure; DBP: Diastolic blood pressure. TC: Total Cholesterol; HDL: high density lipoprotein; TG: Triglycerides; LDL: low density lipoprotein; VLDL: Very low density lipoprotein. The ANOVA test of repeated measures was used in the comparison between IM vs. PEM, PEM vs. PIM, and IM vs. PIM.

\* Statistical significance found.

moment (2 months of intervention), and 4 (1.5 - 5.8 mg/dL) in the post-inactivity moment (2 months of inactivity). Comparisons were made between CRP of IM vs. PEM; PEM vs. PIM; and IM vs. PIM, with a p-value of 0.04. Figure 3C presents the median values at the three moments of collection.

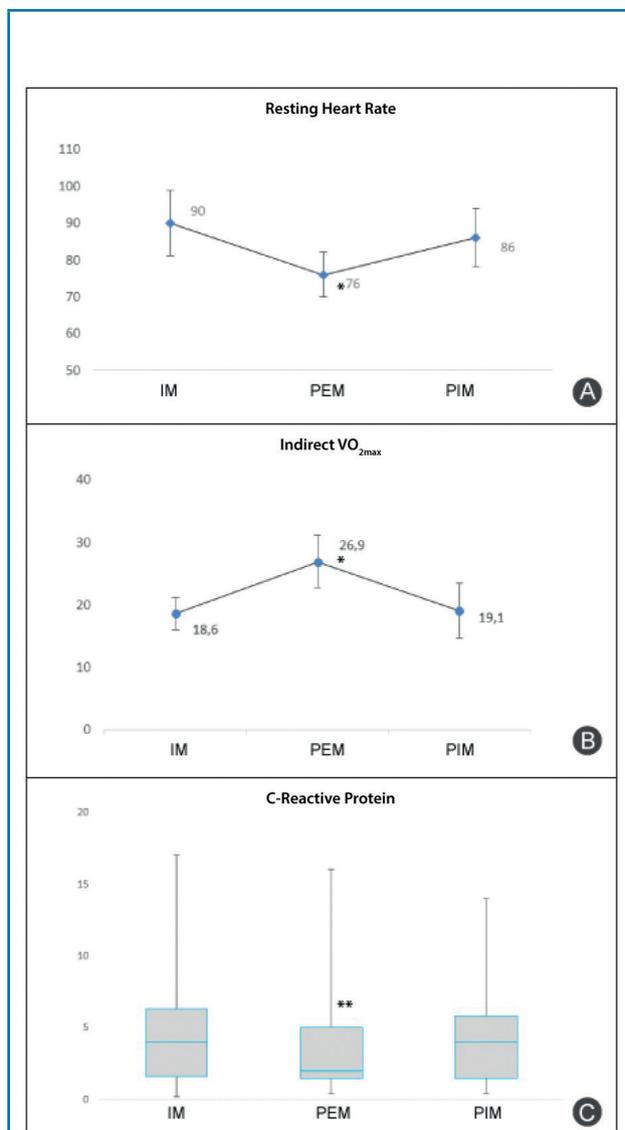
In table 2, it was possible to see that, after crossing the data from IIG and PIG, none of the variables of the lipid profile was modified by the high intensity interval exercise protocol. Values did not change between IM vs. PEM, between PEM vs. PIM, nor between the IM vs. PIM.

## Discussion

In the present study, young women using COC, after the period of high-intensity interval exercise, showed a reduction in resting HR and an increase in indirect  $VO_{2max}$  demonstrating the effectiveness of the program in improving the functional capacity of the participants. However, despite the improvement in indirect  $VO_{2max}$ , no change in the lipid profile was observed, but CRP optimization was detected.

Through previous studies carried out by our group, we were able to verify that women using COC have a higher lipid ( $\uparrow$  LDL,  $\uparrow$  CT,  $\uparrow$  TG)<sup>12</sup> and inflammatory ( $\uparrow$  CRP and  $\uparrow$  oxidized LDL) profiles,<sup>11</sup> especially in those who declared themselves to be irregularly active. Therefore, it is possible to conclude that the implementation of physical exercises in the weekly routine of COC users can modify this.

Some factors may explain the findings of this study, including the fact that the participants are normolipidic. It is well-known that, in the general population, the reduction in triglyceride levels mediated by physical exercise occurs in a sensitive manner in inactive people and with fasting hypertriglyceridemia.<sup>24,25</sup> Regarding total cholesterol and HDL, it was observed that the reduction of its levels occurs when physical exercise is associated with a diet that culminates in a reduction in BMI.<sup>25</sup> Therefore, as the participants in our study were normolipidic and did not undergo any type of dietary restriction during the study period, perhaps because of this, the values of triglycerides and cholesterol-rich lipoproteins were not modified.



**Figure 3 – A:** Mean values and standard deviation of resting heart rate (RHR) in beats per minute (bpm) with cross data between initial intervention group (IIG) and posterior intervention group (PIG), respectively in the initial moment (IM), post-exercise moment (PEM), and post-inactivity moment (PIM). \*  $p < 0.01$  in the ANOVA test of repeated measures with difference between IM vs PEM and PEM vs PIM. **B:** Indirect values of mean and standard deviation of maximum oxygen consumption ( $VO_{2max}$ ) in ml O<sub>2</sub>/Kg/min with crossed data from IIG and PIG in the IM, PEM, and PIM. \*  $p < 0.01$  in the ANOVA test of repeated measures between IM vs. PEM and PEM vs. PIM. **C:** Values for median and interquartile range of C-Reactive Protein (CRP): Data in mg / l, crossed from the IIG and PIG, in the IM, between the PEM and between PIM. \*\*  $p = 0.04$  (Kruskal-Wallis test) in the comparison between IM vs. PEM and between PEM vs. PIM.

In addition, when thinking about physical exercise as a means to obtain gains, it is necessary to consider other issues associated with it, which are fundamental to achieving the proposed objective or not. Such variables as frequency, intensity, modality, and duration of the session are only a few of the factors that can also influence the final result.<sup>26</sup>

For the participants in this study, a specifically designed training included high-intensity, low-volume physical exercise, with a twice-a-week frequency. This type of training was chosen because it fit the participants' life routine and met the basic prerequisites of physical training. In addition, this protocol minimizes the monotony of training and increases adherence, as it is performed only two days a week.<sup>27</sup>

Thus, training was effective in indirectly improving  $VO_{2max}$ , but it was not enough to induce changes in the lipid profile. It is necessary to consider the hypothesis that another type of protocol that was carried out by manipulating the variables in another way could induce changes in the lipid profile. An example of this is the work that analyzed the effect of physical exercise on postprandial lipemia (PPL). In two studies carried out by our research group, different results (without modification and with reduction of the PPL) due to the modification of the exercise protocol were observed.<sup>15,16</sup>

Another important point to be discussed to explain the results of the present study is the caloric expenditure between exercise sessions. According to Kim et al.,<sup>28</sup> for changes in the lipid profile to occur, it is necessary not only to implement physical exercise sessions, but also to increase caloric expenditure between exercise sessions. In their study, it was found that the participants who reduced the PPL were those who received instructions to stay active on a daily basis. With this purpose in mind, participants were included in the routine of avoiding the use of elevators, prioritizing walking as the main means of transport, among other actions that increased daily caloric expenditure and contributed to improving the lipid profile, especially the PPL.

To further reinforce the importance of lifestyle for the lipid profile in COC users, we highlight the observational study that we conducted in 2015. This study identified that physically active women had a fasting lipid profile, PPL, and CRP that were less than irregularly active women.<sup>16</sup> The explanation for these findings may be based on the fact that these women, in addition to exercising regularly, also had an active life, that is, they

developed activities of daily living that promoted greater caloric expenditure.

In addition, people who frequently engage in physical exercise programs usually take greater care with eating habits. The present study did not encourage changes in the participants' lifestyles (higher levels of physical activity between sessions and changes in diet). On the contrary, the participants were asked to maintain their daily routine and eating habits throughout the study.

As for the inflammatory profile, corroborating the findings of our article, a retrospective study published in 2017 demonstrated a directly proportional relationship between heart rate and subclinical inflammation.<sup>29,30</sup> In fact, in our study it was possible to notice both the reduction in resting HR and CRP, which reinforces the thesis that physical exercise was effective in decreasing the inflammatory profile and sympathetic discharge simultaneously. This finding may have other implications, since in the genesis of atherosclerotic disease, sympathetic imbalance, and subclinical inflammation are important.<sup>30</sup>

The improvement of the inflammatory profile results in significant benefits, such as the reduction of oxidized LDL, a lipoprotein that participates in the genesis of atherosclerotic plaque.<sup>31</sup> The failure to measure this variable in our study was a limitation that prevented a deeper analysis of the effect of the exercise program on the reduction of CRP. It is important to highlight, however, that in the Women's Health Study, conducted with postmenopausal women, the increase in the inflammatory profile represented the main risk factor for cardiovascular diseases when compared to other variables, such as the elevated lipid profile and the levels of homocysteine.<sup>32</sup>

Regarding the last study mentioned, in the analysis of subgroups, it was found that even those participants who presented low levels of LDL-cholesterol showed greater risks of developing acute cardiovascular events when they had CRP levels > 3 mg/L.<sup>32</sup> Continuing with this study, it was found that the inflammatory profile remained more sensitive to unwanted cardiovascular outcomes when compared to the lipid profile, represented by LDL-cholesterol.<sup>33</sup>

Therefore, it is possible to hypothesize that the reduction in CRP with the exercise protocol proposed in this study may be crucial in controlling the onset of cardiovascular diseases in the long term, regardless of the reduction in the lipid profile.

Finally, the increase in indirect  $VO_{2max}$  caused by exercise can have other significant benefits. Although a reduction in the lipid profile was not observed, an inverse correlation between  $VO_{2max}$  and cardiovascular diseases and mortality from all causes was observed.<sup>34</sup> In this sense, the increase in  $VO_{2max}$  promoted by the physical exercise program in this population may well represent a long-term reduction in the risk of morbidity and mortality from cardiovascular diseases. We therefore recommend that healthcare professionals encourage the practice of physical exercise in this population as a way to minimize the cardiovascular risk promoted by the use of COC.

Such variables as total caloric expenditure, food intake, and other lifestyle habits also contribute to the improvement of the lipid and inflammatory profile, and should therefore be observed in conjunction with any physical exercise program. Thus, future studies with women using COCs should be conducted, taking into account parameters other than physical training. Furthermore, maximum tests should be used to determine the  $VO_{2max}$  and HR in order to make the exercise prescription more individualized.

This study is noteworthy as it is the first clinical trial with the application of HIIT in women who use COC. The evaluations carried out in this research open discussions on the real effectiveness of exercise on one's lipid profile, which remains within normal limits. In addition, the improvement in inflammatory activity allows us to emphatically recommend physical exercise for this group, as it acts upon a cardiovascular risk factor and reduces the risk for the development of type II diabetes (with insulin resistance), the latter of which has already been demonstrated in women using COC.<sup>35</sup>

## Conclusion

The high intensity interval exercise protocol performed on the treadmill and applied in this study was not able to modify the participants' lipid profile; however, it was able to optimize the inflammatory profile of irregularly active women using COCs.

## Author contributions

Conception and design of the research: Gomes AF, Petto J. Acquisition of data: Sacramento MS, Santa Cecilia LM, Almeida FOB, Jesus DS, Barbosa JS. Analysis and

interpretation of the data: Gomes AF, Petto J. Statistical analysis: Gomes AF, Petto J.

Writing of the manuscript: Gomes AF, Oliveira ECO, Petto J. Critical revision of the manuscript for intellectual content: Petto J.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

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## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade Nobre de Feira de Santana under the protocol number 79549517.3.0000.5654. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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