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Original research

Changes in inflammation markers after a 10-week high-intensity combined strength and endurance training block in women: The effect of hormonal contraceptive use

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ABSTRACT

Objectives: The influence of hormonal contraceptives (HC) on inflammation and body composition after high-intensity combined strength and endurance training was investigated.
Design: Active healthy women formed two training groups: HC users (HCU, n = 9) and those who had never used HC (NHC, n = 9). Training included two strength training sessions and two high-intensity interval training sessions per week for 10 weeks.
Methods: Before (PRE) and after (POST) the training intervention, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) concentrations were measured. Dual-energy X-ray absorptiometry was used to estimate fat mass (FM), abdominal fat mass (aFM), and lean mass (LM).
Results: Circulating concentrations of hs-CRP decreased significantly in the NHC from pre to post with $-0.46\,mg\,l^{-1}$ (95% CI: −0.78, −0.14, p = 0.009, ES = 0.434), whereas a significant increase was observed in HCU from pre to post with $0.89\,mg\,l^{-1}$ (95% CI: 1.66, 0.12, p = 0.048, ES = 1.988) with a significant between-group difference (p = 0.015). In addition, hs-CRP concentration was significantly higher in HCU than in NHC after training (p = 0.036) at post. Lean mass increased significantly more in NHC than in HCU (p = 0.049).
Conclusions: High-intensity combined strength and endurance training can modify inflammation and body composition of women. The present study showed that inflammation, in terms of hs-CRP was higher post training in HCU than NHC, which may be associated with smaller gains in lean mass in response to training.

Practical implications

- High-intensity training reduces inflammation, assessed by hs-CRP, in women who are not using HC.
- It is important to recognize that even if hormonal contraceptives have beneficial effects, including consistent cycle, they might increase inflammation status and influence body composition in terms of gains in lean mass in women training at a high intensity.
- Overall, the high-intensity training is well tolerated by the recreationally active women whether they use HC or not.

1. Introduction

A lack of understanding of sexual dimorphism in scientific exercise and sport medicine literature has led to a deficiency in the understanding of exercise physiology in women. The number of women participating in sports has increased dramatically; however, the relative amount of exercise research performed with women as participants is still quite small. Research on women has been limited, in part, because of the difficult nature of controlling for and following the innate hormonal fluctuations of the menstrual cycle.[1] An additional challenge is that women can modify hormonal fluctuations exogenously by using hormonal contraceptives. Hormonal contraceptives (HC) are the most frequently used type of birth control among young women and are also used in the treatment and management of e.g. acne and menstrual disturbances.[2]

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HCs suppress the endogenous production of estrogen and progesterone, which prevents the mid-cycle surge of gonadotrophins, inhibiting ovulation and possible conception-pregnancy.[3] The sex steroid hormones, estrogen and progesterone, are secreted from the ovaries and to a lesser extent from the adrenal glands in women. Although these hormones primarily function to support reproduction, they have been reported to influence a multitude of other physiological and psychological systems.[4]

Low-grade systemic inflammation is an independent risk factor for several diseases such as type 2 diabetes[5] and atherosclerosis.[6] Numerous factors may influence inflammatory status, including relative adiposity (particularly the abdominal area),[7] physical activity,[8] and HC use.[9] Interestingly, Cauci et al. reported that use of HC elevates low-grade inflammation in female athletes.[10] These authors speculated that this could predispose women athletes to a higher exercise-induced inflammatory response and may even elevate cardiovascular risk. At the same time, exercise has been suggested to be an effective non-pharmacological tool to reduce inflammation. For example, exercise has been associated with improvements in the inflammation state in overweight adults,[11] elderly people[12] as well as in heart disease patients.[13]

Considering the increased number of women participating in high-intensity strength and endurance training while using HC, it is important to investigate the combined effects of these behaviors on inflammatory state and overall health. Thus, it seems prudent to study whether the use of HCs has an effect on the reduction of fat mass (particularly abdominal fat mass), the development of lean mass, and/or the possible favorable changes in inflammatory markers. The information generated through such investigation is potentially useful for prescribing safe and effective guidelines to minimize the potential negative effects of high-intensity exercise training. Therefore, the purpose of this study was to examine the possible influence of HC on changes in inflammation and body composition, including fat mass (FM), abdominal fat mass (aFM), and lean mass after 10 weeks of high-intensity combined strength and endurance training in women.

2. Methods

This study consisted of volunteers recruited from the Jyväskylä region of Finland by a newspaper advertisement, a posting on the website of the Department of Biology of Physical Activity (University of Jyväskylä), and various social media channels. The target group was healthy physically active women. Inclusion criteria were as follows: 18–40 years of age healthy women, body mass index (BMI) <30 kg m^{-2} (excluding pronounced overweight), and a Cooper running test (or equivalent) result of >2300 m. Both women who have at least one year of hormonal contraceptive use (HCU) and who have never used hormonal contraceptives (NHC) were recruited. Hormonal contraception used by the participants consisted of oral monophasic combined pills (ethinyloestradiol and progestins in different doses). In addition, one participant had an intrauterine (hormonal) system. All HCU participants had at least two years of hormonal contraceptive use.

Participants were examined before and after 10 weeks of high-intensity combined strength and endurance training. A total of four high intensity training sessions per week were performed by each participant and consisted of two strength training sessions and two running interval training sessions. Strength training was planned for runners and thus targeted the lower extremities but included core and upper-body exercises as well. Every strength training session consisted of several multi-joint movements with progressively increasing loads from 50 to 85% 1 RM during the training period. The main exercises included maximal and explosive sets of squat, bilateral leg press, knee flexion, calf raise, and calf jump (2–3 sets/movement and 6–10 repetitions/set). The main exercises were followed by plyometric exercises without external load: drop jumps, plyometric strides, step-ups and hurdle-jumps (2 sets/movement and 6–10 repetitions/set), and core exercises (6 sets and 10–15 repetitions/set). Endurance training sessions each week consisted of one high-intensity interval training session with 4 × 4 min running intervals progressing in intensity from +70% HRmax to 90% of HRmax over the course of the 10-week training period (4 min rest during which HR returned to 60–70% HRmax), and one sprint training session with 3 × 3 × 100 m all-out sprints (2 min rest during which HR returned to 60–70% HRmax/5 min between sets). In addition, participants were to complete one higher-volume (≥2 h) low-intensity aerobic exercise every week.[14]

Ethical approval of both methodology and consent procedures was granted by the University of Jyväskylä Ethical Committee. The study was conducted according to the provisions of the most recent Declaration of Helsinki. Prior to participation, study participants received written and oral information about the study design and measurement procedures. In addition, possible risks and benefits of participation in the study were thoroughly explained prior to participants signing an informed consent document. All participants completed health questionnaires and resting ECG and that were subsequently screened and approved by a medical doctor.

Height of each participant was measured using standard clinical methods. Whole body composition was estimated by Dual X-ray Absorptiometry (LUNAR Prodigy, GE Medical Systems, Madison, USA). The DXA-scans were performed in the morning with the participant in a fasted (12 h) state. Automatic analyses (Encore-software, version 14.10.022) provided total body fat mass and total body lean mass. Abdominal fat was calculated manually.[15] This customized range was then copied to the DXA scans at PRE and POST, respectively.

Blood samples in a fasted state were collected into serum tubes (Venosafe, Terumo Medical Co., Leuven, Belgium) by a qualified lab technician who reviewed analyses of the basic blood count and neutrophils and lymphocytes (Sysmex KX-21N, Kobe, Japan) to check for abnormalities prior to testing that might have indicated possible illness (e.g. acute infection), which may have affected the inflammation data. Participants were instructed to abstain from strenuous physical activity 48 h before the blood samples were taken. Participant reported not having upper respiratory tract infection symptoms for two weeks prior testing. The samples were centrifuged for 10 min at +4 °C with 2000 × *g* (Megafuge 1.0 R, Heraeus, Germany) and followed by immediate spectrophotometry analyzes (Konelab 20XTi, Thermo Fisher Scientific, Vantaa, Finland) for total cholesterol (Chol), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides. Serum was kept at −80 °C until analyzed for serum high sensitive-C reactive protein (hs-CRP), Tumor-necrosis-factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) using the Immulite 1000 and immunoassay kits (Immulite, Siemens, IL). The detection limits and inter-assay coefficients of variation, respectively, were 0.1 pg ml^{-1} and 10% for hs-CRP, 2.0 pg ml^{-1} and 3.8% for TNF-α, 1.5 pg ml^{-1} and 2.8% for IL-1β, 0.2 pg ml^{-1}, and 3.4% for IL-6.

The menstrual cycle phases were self-estimated estimated from the first day of menstrual bleeding (day 1). Participants were instructed to contact the laboratory to schedule blood and performance measurements between days 1–5 of the cycle. When hormonal analysis was completed, results that indicated ovulation were omitted. The cycle length in NHC group was 28 to 35 days. Similarly, the HCU group was measured between days 1–5 of their cycle.

All statistics were performed using SPSS for Windows (IBM SPSS version 24.0; SPSS Inc., Chicago, IL). Conventional statistical methods were used to obtain means, standard deviation (SD), 95% confidence intervals (95% CI), and Pearson's product moment

Table 1
Mean (SD) changes in body composition and serum health markers from baseline to post-intervention.

		Baseline (PRE)	Post-intervention (POST)	Change from the baseline to post-intervention (95% CI)	Between group P value
Body mass (kg)	NHC	60.1 (5.8)	59.3 (5.3)	−0.12 (−0.84, 0.60)	0.201
	HCU	59.3 (5.3)	59.0 (5.3)	−0.32 (−1.12, 0.48)	
Total fat mass (kg)	NHC	14.1 (5.3)	13.1 (4.5)*	−0.99 (−1.87, −0.11)	0.111
	HCU	13.3 (4.5)	12.6 (4.4)	−0.76 (−1.60, 0.079)	
Abdominal fat mass (g)	NHC	955 (629)	845 (565)*	−110 (−207, −13)	0.187
	HCU	881 (484)	813 (468)	−68 (−179, 43)	
Lean mass (kg)	NHC	43.8 (2.6)	44.7 (2.8)*	0.91 (0.55, 1.26)	0.049
	HCU	43.1 (4.5)	43.4 (4.2)	0.39 (−0.68, 0.85)	
Total cholesterol (mmol l^{-1})	NHC	5.34 (0.74)	5.14 (0.69)*	−0.21 (−0.60, 0.18)	0.678
	HCU	(0.78)	4.72 (0.74)	−0.09 (−0.58, 0.40)	
HDL(mmol l^{-1})	NHC	1.98 (0.45)	2.05 (0.32)	0.07 (−0.15, 0.29)	0.839
	HCU	1.84 (0.34)	1.97 (0.45)	0.13 (−0.18, 0.44)	
LDL (mmol l^{-1})	NHC	2.83 (0.87)	2.63 (0.67)	−0.19 (−0.43, 0.05)	0.273
	HCU	2.31 (0.51)	2.45 (0.54)	0.10 (−0.48, 0.28)	
Triglycerides (mmol l^{-1})	NHC	(0.14)	0.80 (0.31)	0.08 (−0.10, 0.26)	0.789
	HCU	(0.37)	0.89(0.34)	0.00 (−0.18, 0.18)	
Blood glucose (mmol l^{-1})	NHC	5.11 (0.31)	5.33 (0.27)	0.22 (−0.04, 0.49)	0.526
	HCU	4.89 (0.41)	5.37 (0.67)	0.38 (−0.13, 0.91)	

CI, confidence intervals; *Statistically significant change from the baseline adjusted with baseline values; $p < 0.05$. NHC = women who have never used hormonal contraceptives, HCU = women who have at least one year of hormonal contraceptive use HDL = high-density lipoprotein, LDL = low-density lipoprotein.

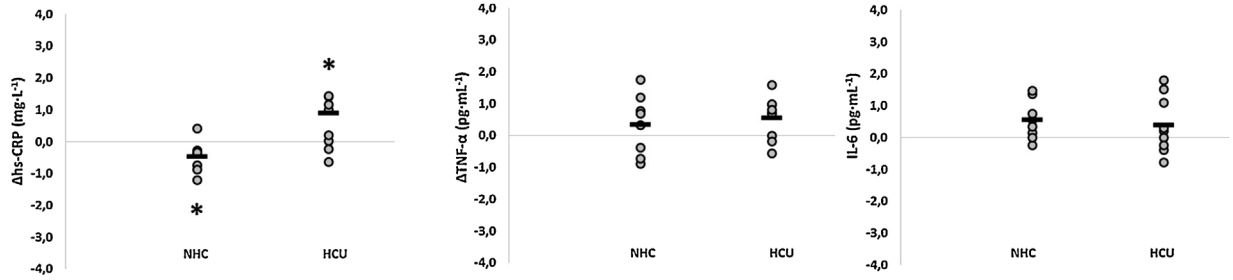

Fig. 1. Changes in serum high-sensitive C-reactive protein (hs-CRP), Tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) concentrations from pre to post. Each participant (within each group) is represented by an O. The horizontal line represents the group mean (*$p < 0.05$ versus baseline). NHC = women who have never used hormonal contraceptives, HCU = women who have at least one year of hormonal contraceptive use.

correlation coefficients. One-way analysis of variance was used to compare continuous variables between groups at baseline and post-intervention and within groups comparisons were done using paired samples T-test. Univariate general linear model covariance analysis (ANCOVA) was used to test differences between groups, with the difference (Δ-value) as the dependent factor, group variable as the fixed factor, and baseline values as covariates. All data are reported as means and standard deviations and statistical significance was set at $p \leq 0.05$. Effect sizes (ES) are expressed using Cohen's d such that when $d \geq 0.20$ ES was considered to be small, when $d \geq 0.50$ ES was considered to be medium, and when $d \geq 0.80$ ES was considered to be large.[16]

3. Results

Training compliance for the training intervention was high with both groups completing an average of 97% of the 37 training sessions. Training intensity for all sessions was monitored such that the prescribed training and progression were achieved i.e. no marked deviation from the prescribed training was observed.

Changes in body composition and serum health markers are summarized in Table 1 and have been partly reported elsewhere.[14] No significant changes were observed in body weight in either of the groups. FM decreased significantly by 1.0 kg (95% CI: −1.9, −0.1, $p = 0.032$, ES = 0.203) in NHC, whereas in the HCU the magnitude of change was similar with a decrease of 0.8 kg (95% CI: −1.6, 0.1) but this finding was non-significant ($p = 0.068$, ES = 0.157). There was no between-group difference in change in fat mass. Similarly, aFM decreased significantly only in NHC by 0.11 kg (95% CI: −0.21, −0.01, $p = 0.048$, ES = 0.184), whereas no significant difference was observed in aFM of HCU, which decreased by 0.07 kg (95% CI: −0.2, 0, $p = 0.150$, ES = 0.143). LM increased significantly by 0.9 kg (95% CI: 0.55, 1.26, $p < 0.001$, ES = 0.333) in NHC, whereas a non-significant increase of 0.4 kg (95% CI: -0.7, 0.9, $p = 0.101$, ES = 0.171) was observed in LM of HCU with a significant between-group difference ($p = 0.049$).

A decrease in total cholesterol of −0.21 mmol l^{-1} (95% CI: −0.60, 0.18, $p = 0.050$, ES = 0.560) was observed in NHC while no significant effect of exercise training on HDL, LDL, triglycerides or glucose was observed in either of the groups. No significant differences between the groups was observed in these measures either.

Individual changes in circulating hs-CRP, IL-6, and TNF-α concentrations are presented in Fig. 1. Circulating concentrations of hs-CRP decreased significantly in NHC from pre to post by 0.46 mg l^{-1} (95% CI: −0.78, −0.14, $p = 0.009$, ES = 0.434), whereas a significant increase w in HCU from pre to post of 0.89 mg l^{-1} (95% CI: 1.66, 0.12, $p = 0.048$, ES = 1.988) was observed and accompanied by a significant between-group difference ($p = 0.015$). In addition, CRP concentration was significantly higher in HCU than in NHC at post ($p = 0.036$). Circulating TNF-α, IL-1β, and IL-6 concentrations were unaffected by exercise and no between-group differences were observed.

There were no significant correlations between changes in body composition and inflammation markers when all the participants were considered as a one group. Furthermore, changes in fat mass or lean mass did not correlate with changes in inflammation markers in HCU, however, a significant correlation between

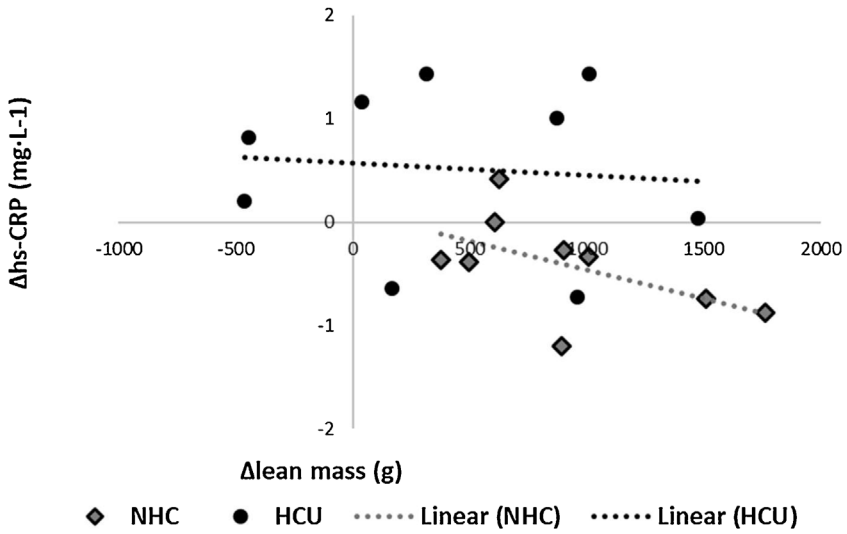

Fig. 2. Change in serum hs-CRP correlated negatively with changes in lean mass in NHC (grey square) whereas a significant correlation was not observed in HCU (black circle) group. NHC = women who have never used hormonal contraceptives, HCU = women who have at least one year of hormonal contraceptive use.

hs-CRP changes and changes in lean mass were observed in NHC ($r = -0.700$, $p = 0.036$; see Fig. 2).

4. Discussion

The main objective of the present study was to evaluate the effect of hormonal contraceptives on high-intensity combined strength and endurance training induced changes in inflammation and body composition in healthy women. The primary finding of the study was that the inflammatory responses to combined high-intensity training may be modified by HCU in young women. In the present study, inflammation status, assessed by circulating hs-CRP concentration, decreased in women not using HC, increased in women using HC, and was significantly higher post-training in HCU than NHC. These results indicate that HC use may influence high-intensity training induced inflammatory adaptation and related responses. Secondly, there were no significant differences between groups in training induced changes in total or abdominal fat mass, although only NHC showed a significant decrease in total and abdominal fat mass. Likewise, lean mass increased significantly in NHC, but not in HCU, and was greater by the end of the study in NHC than HCU.

C-reactive protein is widely used marker of health and even modest increases in hs-CRP have been linked to an increased risk of atherothrombotic events.[17] In the present study there was a significant reduction in hs-CRP concentration in NHC ($\Delta = -0.46\ mg\ l^{-1}$), whereas in HCU a significant increase was observed ($\Delta = 0.89\ mg\ l^{-1}$). Differences in hs-CRP adaptations could be related to changes in body composition.[18] Although the decrease in fat mass and abdominal fat mass were significant only in NHC, the absolute changes in fat mass were similar in both groups and there were no statistically significant differences between HCU and NHC. Indeed 7 out of 9 participants in NHC, and 6 out of 9 participants in HCU reduced whole-body fat mass. Another notable aspect of the present study was that the magnitude of changes in fat mass in the present study were modest, -1.0 ± 1.1 kg in NHC and -0.8 ± 1.0 kg in HCU. Thus, the different changes in body composition do not fully explain the divergent hs-CRP responses in HCU and NHC.

Previous studies have found combined endurance and strength training to be effective for increasing lean mass.[19] This study suggests that using HC could have an effect on such training induced gains in lean mass in physically active women. Furthermore, change in lean mass could be one of the mediators of changes in inflammation status. In fact, Sardeli et al. suggested that the physiological mechanisms explaining beneficial effects of increased muscle mass on inflammation could be that increased muscle mass influences energy expenditure,[20] and higher muscle mass has more potential to produce anti-inflammatory myokines during an acute exercise bout.[21]

There is evidence suggesting that exercise training has long-term anti-inflammatory effects, although a single bout of exercise may lead to transient increase in inflammatory markers, such as pro-inflammatory cytokines.[22] The inflammatory effect of exercise is highly dependent on training intensity and duration, fitness level, exercise mode, and nutritional status of individuals.[23] Cauci et al., however, reported that women athletes using oral contraceptives have markedly elevated low-grade inflammation assessed by circulating hs-CRP.[10] These authors have previously reported similar results to the present ones; i.e., higher hs-CRP concentration in an athletic population of hormonal contraceptive users as well as in general population users.[24] Interestingly, the prevalence of female athletes classified as high risk ($>3.0\ mg\ l^{-1}$) in terms of hs-CRP concentrations was higher than in the general population.[10] Cauci et al.[10] concluded that sporting activity seems to have some anti-inflammatory effect, but this relationship is lost in HC users. In the present study, high-intensity combined strength and endurance training led to significantly different outcomes in hs-CRP concentrations in the NHC and HCU. While speculative, we suggest that HC use affects and interacts with responses to high-intensity training as intensity is one of the key mediators of the exercise-induced changes in inflammation markers.[23]

In the present study, there was no significant difference between hs-CRP concentrations between groups before the intervention, whereas hs-CRP concentration was significantly higher after 10 weeks of training in HCU than in NHC. Previous studies have reported that exogenous hormones within HC women tend to elevate CRP concentration,[25] while endogenous estrogen decreases and progesterone increases CRP concentrations.[26] Van Rooijen et al. reported that two months of combined oral contraceptives led to a significant increase in serum hs-CRP, as median levels increased from $0.45\ mg\ l^{-1}$ to $1.48\ mg\ l^{-1}$ with second generation and to $2.02\ mg\ l^{-1}$ with third generation combination contraceptive pills.[27] These authors propose that with HC use there is a direct effect on hepatocyte CRP synthesis invoking the observed increase, and not secondary mediated events (e.g., via IL-6, and both IL-6 and TNF-α remained statistically unaltered in the cur-

rent study). In the present study, HCU had used HC for at least two years thus, changes in hs-CRP cannot be attributed starting the use of HC. It should be noted that although an increase in CRP concentrations were observed in HCU, concentrations mostly remained below the 3.0 ml l^{-1} cut-off point that indicates a high risk of cardiovascular disease.[28] Nevertheless, the hs-CRP allowed us to classify most of the participants to be at "moderate cardiovascular risk" (1.0–3.0 mg l^{-1}) prior to commencement of the study in both groups (NHC 7 out of 9 and HCU 8 out of 9). At POST, hs-CRP was reduced to the level of "low cardiovascular risk" (<1.0 mg l^{-1}) in eight out of nine participants in NHC, whereas only two in HCU group could be classified as having "low cardiovascular risk".[28]

The current study had three major limitations — (1) use of varying HC products, (2) use of only the follicular phase of the menstrual cycle for performance and hormonal testing, (3) limited number of participants, and (4) an incompleteness of dietary and training information. When evaluating the present findings one should remember that three HC formulations were used in this study: combined pills (seven participants), progesterone only pills (one participant), and intrauterine (hormonal) systems (one participant), which all have different active ingredients and amounts of exogenous hormones. Although all these formulations were all monophasic, the impact of different formulations on performance- or training-induced adaptations may vary (and is in need of investigation); thus, it is not possible to determine the specific effects of individual formulations on training-induced changes in inflammation markers or in body composition. The purpose of this study, however, was to examine the general effects of HC on a 10-week combined strength and endurance training period rather than to single out a specific HC formulation. The present study measured participants only once during the early follicular phase of their cycle between days 1 and 5, thus it should be acknowledged that some of the measured variables might be influenced by different phases of the cycle.[4] Nevertheless, reliable comparisons between pre and post evaluations could be made due to completing measurements in the same phase before and after the intervention. The sample size in the present study was indeed rather small (HCU: n = 9, NHC: n = 9), however, the groups were homogenous in terms of body composition and performance prior the study and the sample size is in line with previous studies on combined strength and endurance training. Lastly, we acknowledge that dietary quality might be affected by HC usage or menstrual cycle phase,[29] and is known to affect and modulate health related biomarkers. Future work should attempt to include dietary information.

5. Conclusion

Even if hormonal contraceptives provide a consistent cycle and eliminate menstrual irregularities, they might have an effect on the inflammation status of the women undergoing high-intensity exercise training. Furthermore, the data indicates that HC may influence training-induced gains in muscle mass, and have a small influence on decrease in fat mass, which may be of interest to even recreationally active women. Thus, there is a need for well-controlled investigations that take into consideration HC use and menstrual cycle phases in combined strength and endurance training to ensure that exercise prescription, particularly in athletic women, is optimized.

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