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ORIGINAL ARTICLE

Sport-based physical activity recommendations and modifications in C-reactive protein and arterial thickness

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Abstract

We analyzed the effects of 1 year of engagement in ≥ 300 min/week of organized sports on inflammatory levels and vascular structure in adolescents. The sample was composed of 89 adolescents (11.6 ± 0.7 years old [43 boys and 46 girls]), stratified according to engagement in ≥ 300 min/week of sport practice during at least 12 months of follow-up ($n = 15$, sport practice; $n = 74$, non-sport practice). Arterial thickness (carotid and femoral) was assessed by ultrasound scan, while high sensitive C-reactive protein levels were used to assess inflammatory status. Trunk fatness (densitometry scanner), biological maturation (age at peak height velocity), blood pressure, and skipping breakfast were treated as covariates. Independently of body fatness and biological maturation, the group engaged in sports presented a higher reduction in C-reactive protein (mean difference −1.559 mg/L [95%CI −2.539 to −0.579]) than the non-sport group (mean difference −0.414 mg/L [95%CI −0.846 to 0.017]) ($p = 0.040$). There was a significant relationship between changes in C-reactive protein and changes in femoral intima-media thickness in the non-sport group ($r = 0.311$ [95%CI 0.026 to 0.549]).

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Conclusion: Inflammation decreased in adolescents engaged in organized sports, independently of trunk fatness and biological maturation. Moreover, inflammation was related to arterial thickening only in adolescents not engaged in sports.

What is Known:
- *Intima media thickness is a relevant marker of cardiovascular disease in pediatric groups, being affected by obesity and inflammation.*
- *The importance of monitoring inflammatory markers from childhood is enhanced by the fact that alterations in these inflammatory markers in early life predict inflammation and alterations in carotid IMT in adulthood.*

What is New:
- *Anti-inflammatory properties related to physical exercise performed at moderate intensity, on inflammation and alterations in IMT are not clear in pediatric groups.*
- *Due to the importance that sport participation has assumed as a promoter of improvements in health and quality of life, it is necessary to understand its potential benefits for cardiovascular health during human growth.*

Keywords Adolescent · Inflammation · Arterial thickness · Cardiovascular health

Abbreviations

APHV	Age at peak height velocity
CRP	C-reactive protein
CIMT	Carotid intima media thickness
DBP	Diastolic blood pressure
FIMT	Femoral intima media thickness
IMT	Intima media thickness
SBP	Systolic blood pressure
TF	Trunk fatness

Introduction

Intima media thickness (IMT) is a relevant marker of cardiovascular risk [8, 13], being affected by obesity and inflammation [2, 8, 13]. Childhood obesity plays a central role in the development of cardiovascular complications [8, 11], while inflammatory processes are relevant pathways by which obesity is able to produce this effect [11, 13].

Faced with an alarming rate of childhood obesity and its health-related complications, health organizations have developed guidelines to support actions targeting the promotion of a healthy diet and sufficient physical activity among young people [7, 24]. Regarding physical exercise, at least 60 min per day of moderate-to-vigorous intensity (≥ 300 min/week) is recommended [7], and sport participation is one of the most relevant manifestations of physical exercise during this period of life, being an important way to achieve this recommendation [7, 24].

However, the impact of sport participation on inflammation [2, 10] and IMT [21] remains unclear among young people, mainly due to gaps in the literature. The role of the interrelationship between intensity and volume on inflammation is not clear [21], in addition to which the majority of studies assessing the relationship between sport participation and inflammation/IMT are cross-sectional [2, 21], discriminating adiposity through anthropometric tools [3, 22], and generally not taking biological maturation into account [10].

Therefore, due to the importance that sport participation has assumed in modern society as a promoter of health and quality of life in children and adolescents, it is necessary to understand its potential benefits for cardiovascular health during human growth. Thus, the objective of this study was to analyze the effects of 1 year of engagement in ≥ 300 min/week of organized sports on C-reactive protein (CRP) levels and IMT in adolescents.

Methods

Sample

The study is part of a longitudinal study carried out between 2013 and 2014 in the city of Presidente Prudente, Sao Paulo State, Brazil (approved by the Ethics Committee for Research involving human subjects of the Sao Paulo State University—UNESP [process: 322.650/2013]).

Additional information about the sampling process is presented in previous publications [2, 3]. Briefly, seven schools were selected to participate, of which three principals authorized the realization of the study. The inclusion criteria were as follows: (a) aged between 11 and 14 years, (b) regularly enrolled in the school unit, (c) absence of any known diseases, (d) no regular medicine use, and (e) written informed consent statement signed by the parents or legal guardians.

All students of 11–14 years were invited ($n = 495$), and 127 adolescents agreed to participate, fulfilled all inclusion criteria, and returned the written consent form signed. Subsequently, seven adolescents decided to leave the cohort study prior to the baseline measures. Thus, the baseline measures were composed of 120 volunteers and after 12 months of follow-up, 89 adolescents (46 boys and 43 girls) (Fig. 1).

At baseline, the 31 adolescents who dropped out of the study were similar to the 89 remaining adolescents, in terms of biological maturation ($p = 0.067$), femoral IMT ([FIMT] $p = 0.930$), carotid IMT ([CIMT] $p = 0.654$), CRP ($p = 0.352$), trunk fatness ([TF] $p = 0.356$), and systolic ([SBP]

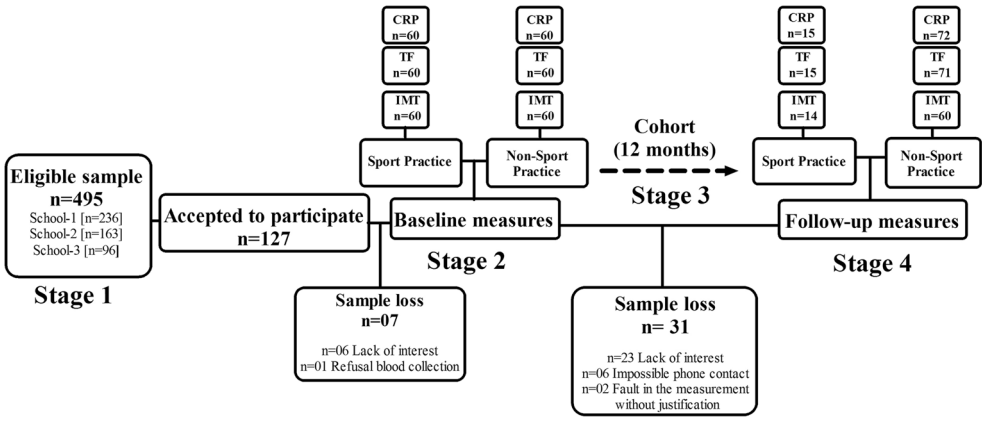

Fig. 1 Flowchart of the sampling process

$p = 0.948$) and diastolic blood pressure ([DBP] $p = 0.944$). Chronological age was slightly higher in the dropout group (dropout 11.9 ± 0.8 versus remaining 11.6 ± 0.7; $p = 0.045$).

C-reactive protein

Biochemical analyses of blood samples were performed in a private laboratory. A 12-h fasting blood sample was collected and CRP was determined through the turbidimetric method (LABEST brand, model LabMax 240).

Arterial thickness

CIMT and FIMT were measured (right side) using an ultrasound scan (brand Philips, model Philips HD 11 XE, Barueri, Brazil), equipped with a high resolution, multi-frequency linear transducer, adjusted to 12 MHz, in a private hospital. The measurements were performed on pictures frozen on the R wave and all images were recorded from the far wall of the arteries in end-diastole [22]. During this examination of the carotid artery, the neck was lightly hyperextended and inclined to reach an angle of approximately 45°. In parallel, during the measure of the femoral artery, the leg was extended on the stretcher, and the measure was taken near the inguinal line [20]. Reproducibility measures were provided by CIMT (intraclass correlation coefficient 0.57; $p = 0.029$) and FIMT (intraclass correlation coefficient 0.91; $p = 0.001$) in 16 adolescents. The same medical doctor was responsible for the clinical measurements at both moments of the research, and did not know which group the adolescents were included in. Standardized values (standard deviation score [SDS]) of CIMT and FIMT were calculated [12].

Engagement in sport practice

Sport participation was assessed through face-to-face interview using the following questions: (1) Outside school, are you engaged in any organized sport practice? If yes: (1.1) What is your perception about the intensity of this sport activity: light, moderate, or vigorous? (1.2) How many days per week do you engage in this sport activity? (1.3) How many hours per day do you expend on this sport activity?

Adolescents were classified as "Sport practice" when engaged in sports of moderate/vigorous intensity for at least 300 min per week in both assessment moments of the study [7]. At baseline, 60 adolescents were classified as "Sport practice" and 60 adolescents were classified as "Non-sport practice." At follow-up, "Sport practice" had 31 dropouts: 14 adolescents quit the sport, were assessed at follow-up, and classified as "Non-sport practice" and 17 adolescents abandoned the study (3 absences from the previously scheduled assessment without clear justification and the desire to quit due to lack of time to participate in the measures due to competitions). At baseline, the 31 dropouts were similar to the 15 remaining adolescents in the Sport practice group, in terms of age ($p = 0.078$), biological maturation ($p = 0.128$), FIMT ($p = 0.225$), CIMT ($p = 0.888$), CRP ($p = 0.174$), SBP ($p = 0.727$), and DBP ($p = 0.672$), while TF was lower in the remaining adolescents ($p = 0.035$). There were no dropouts in the "Non-sport practice group."

In the longitudinal analysis, there were two groups: "Sport practice" ($n = 15$, adolescents who achieved ≥ 300 min/week of moderate/vigorous intensity at both moments) and "Non-sport practice" ($n = 74$, adolescents with no sport participation at both moments [$n = 60$], and adolescents who quit the sport between baseline and follow-up [$n = 14$]). At baseline, the Sport practice group presented a previous engagement of 61.7 months (95%CI = 44.6 to 78.8) and weekly training of 603 min (95%CI = 449.8 to 756.1). The adolescents were engaged in swimming ($n = 6$), soccer ($n = 6$), basketball ($n = 1$), handball ($n = 1$), and dance ($n = 1$).

Additionally, to quantify the effectiveness of the sport classification used in the study, the amount of habitual physical activity was estimated over seven consecutive days through the use of pedometers (brand Yamax Digiwalker, model SW200) fixed to the clothes near the hip. The number of steps was higher in the "Sport practice" group than the "Non-sport practice" group at baseline (Sport $12{,}965 \pm 4540$ versus Non-

sport 8814 ± 3689; $p = 0.001$) and follow-up (Sport 12,944 ± 4601 versus Non-sport 9540 ± 4151; $p = 0.006$).

Covariates

Data regarding sex, skipping breakfast, and chronological age were registered through a face-to-face interview. Body mass was measured on a digital scale (brand Filizola, model Personal Line 200) with a precision of 0.1 kg. Height was measured using a stadiometer (brand Sanny, model Professional, Brazil) with a precision of 0.1 cm (body mass index [BMI] was calculated as follows: body mass / height^2 [kg/m^2]). Waist circumference (WC) was measured using a anthropometric measure tape (brand Sanny, model Professional, Brazil) with a precision of 0.1 mm. Biological maturation was estimated through the age at peak height velocity (APHV) using previously validated equations [16]. SDS of BMI and WC were calculated.

SBP and DBP were assessed using an automatic device (model HEM 742 INT; Omron Healthcare Inc. Intellisense, Bannockburn, Illinois, USA), validated by Christofaro et al. [5]. Measurements were taken three times and the average of the final two measurements was considered as the blood pressure [17].

Trunk fatness (TF) was estimated using a densitometry scanner (brand General Electrics, model Lunar—DPX-NT, General Electric Healthcare, Little Chalfont, Buckinghamshire, UK) and values were presented in percentage. This measure was performed on the whole body and the volunteers wore no shoes or metal objects. Trunk fatness was estimated using the software GE Medical System Lunar (version 4.7).

Statistical analysis

Numerical variables are presented as mean and 95% confidence intervals (95%CI). The CRP is presented under logarithm transformation due to non-parametric distribution. Baseline characteristics were compared according to sport practice (yes or no), using the Student *t* test (Table 1). Absolute changes over time were compared between the Sport participation and Non-sport participation groups using analysis of covariance (ANCOVA [Fig. 2]) [17]. ANCOVA models were adjusted by sex, age (baseline), trunk fatness (baseline and mean difference), maturity offset (baseline and mean difference), SBP (baseline), DBP (baseline), skipping breakfast (number of days/per week), and baseline value of the dependent variable (FIMT, CMIT, and CRP) [25]. In the multivariate models created by ANCOVA, the Levene's test assessed the homogeneity of the variances ($p > 0.05$ denotes adequate goodness of fit). The Eta-squared (ES-r) was utilized to express measures of effect size: small effect size, < 0.060; moderate effect size, 0.060 to 0.139; and large effect size, ≥ 0.140 [14].

The Pearson correlation (*r*) and its 95%CI tested the relationship between the mean differences, while partial correlation analyzed the same relationships adjusted by sex, age [baseline], APHV [baseline], and trunk fatness [baseline] (Fig. 2). Statistical significance was set at a *p* value lower than 0.05 and analyzed using the software BioEstat (version 5.0).

Results

After 12 months of follow-up, 89 adolescents remained in the study and were assessed at the follow-up moment. At baseline, boys and girls were different in terms of TF ($p = 0.022$), while the groups of adolescents who were engaged and non-engaged in sport practice were similar in all analyzed variables (Table 1).

ANCOVA verified that adolescents engaged in sports presented a greater reduction in CRP (mean difference −1.559 mg/L [95%CI −2.539 to −0.579]) than the non-sport group (mean difference −0.414 mg/L [95%CI −0.846 to 0.017]) ($p = 0.040$; ES-$r = 0.056$ [small effect size]) (Table 2). In this multivariate model, biological maturation ($p = 0.001$; ES-$r = 0.140$ [large effect size]), DBP ($p = 0.151$; ES-$r = 0.077$ [moderate effect size]), and baseline value of CRP ($p = 0.001$; ES-$r = 0.366$ [large effect size]) affected the changes in CRP (the multivariate model was adequately fitted [Levene's test]). Although adolescents engaged in sports presented a significant reduction in FIMT, ANCOVA identified that absolute changes in FIMT ($p = 0.127$) and CIMT ($p = 0.518$) were similar between the Sport Practice and Non-Sport Practice groups. Absolute changes in all values converted into SDS were similar between the Sport Practice and Non-Sport Practice groups.

After adjustment (sex, age [baseline], APHV [baseline], and trunk fatness [baseline]), there were significant relationships between mean differences in CRP and FIMT in the overall sample ($r = 0.266$ [95%CI 0.026 to 0.477]) and non-active group ($r = 0.313$ [95%CI 0.044 to 0.540]), but not in the active group (Fig. 2). There was no significant relationship between changes in CRP and CIMT.

Discussion

This is a longitudinal study with adolescents of both sexes, in which sport participation affected the longitudinal relationship between inflammation and IMT. The role of physical exercise in CRP is inconclusive in pediatric populations [10, 15, 23] and has been investigated mainly in obese groups [4, 10, 15, 23]. In obese children and adolescents, a recent meta-analysis did not find a significant impact of physical exercise on CRP

Table 1 General characteristics of the adolescents at baseline according to 1-year sports participation (Presidente Prudente, Sao Paulo, Brazil, 2013–2014)

Variables	Non-sport practice ($n = 74$) Mean (SD)	Sport practice ($n = 15$) Mean (SD)	P value
Sex (boys/girls)	34/40	10/5	–
Age (years)	11.68 (0.72)	11.53 (0.74)	0.491
Weight (kg)	50.88 (13.16)	49.31 (15.11)	0.680
Height (m)	1.54 (0.07)	1.54 (0.06)	0.771
BMI (kg/m^2)	20.96 (4.4)	20.42 (4.95)	0.675
BMI-SDS	0.02 (0.98)	−0.09 (1.09)	0.675
APHV (years)	−2.44 (0.81)	−2.46 (0.71)	0.926
TF (%)	32.69 (11.68)	26.38 (11.53)	0.059
SBP (mmHg)	111.10 (11.22)	112.71 (10.82)	0.603
DBP (mmHg)	68.11 (11.31)	69.40 (8.21)	0.598
CRP (mg/L) $_{log10}$	−0.21 (0.54)	−0.14 (0.76)	0.744
CIMT (mm)	0.46 (0.04)	0.45 (0.04)	0.824
CIMT-SDS	0.01 (1.02)	−0.05 (0.90)	0.824
FIMT (mm)	0.39 (0.08)	0.36 (0.05)	0.184
FIMT-SDS	0.06 (1.04)	−0.31 (0.66)	0.184
WC (cm)	69.9 (10.7)	69.3 (13.0)	0.847
WC-SDS	−0.02 (0.97)	−0.08 (1.17)	0.847

SD standard deviation, *SDS* standard deviation score, *CRP* C-reactive protein, *CIMT* carotid intima-media thickness, *FIMT* femoral intima-media thickness, *TF* trunk fatness, *APVH* peak height velocity, *BMI* body mass index, *WC* waist circumference, *p value* statistical significance, *log10* number under logarithm transformation

levels [10], disagreeing with our findings. Methodological aspects could justify this difference.

First, the systematic review found only nine randomized clinical trials and none of them had exercise protocols achieving ≥ 300 min/week of moderate-vigorous intensity. Moreover, the duration ranged from 8 to 24 weeks and sport participation constituted the intervention of only five studies. In our study, with 48 weeks of follow-up during which physical activity recommendations were achieved, the chronic effect of sport participation on IL-6 would explain, at least in part, the reduced CRP [21]. Moreover, nitric oxide is prone to modifications under prolonged routines of physical exercise, affecting pathways linked to inflammatory response [19]. Our findings denote that adiposity-independent pathways help explain the observed reduction in CRP values in this non-obese sample. Therefore, the combination of long engagement in sports and achieving the current physical activity recommendations seems relevant to decrease the inflammatory

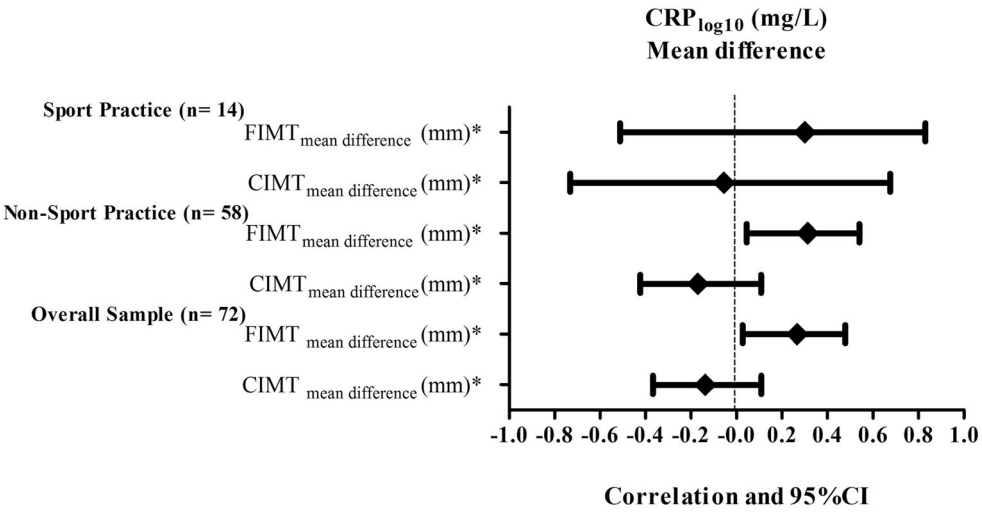

Fig. 2 Partial correlation between changes in inflammation and changes in vascular structure in adolescents according to sport participation (Presidente Prudente, Sao Paulo, Brazil, 2013–2014)

Table 2 Absolute changes (Δ) in anthropometric, metabolic, and cardiovascular variables according to 1-year sports participation among adolescents (Presidente Prudente, Sao Paulo, Brazil, 2013–2014)

Variables	Non-sport practice ($n = 74$)	Sport practice ($n = 15$)	ANCOVA[a]	
	Mean (95%CI)	Mean (95%CI)	*P* value	ES-r [effect size]
Sex (boys/girls)	34/40	10/5	–	–
Weight (kg)	4.995 (4.141 to 5.849)	4.977 (3.048 to 6.907)	0.987	0.001 [trivial]
BMI (kg/m^2)	0.484 (0.175 to 0.792)	0.464 (−0.235 to 1.164)	0.961	0.001 [trivial]
BMI-SDS	−0.011 (−0.076 to 0.055)	−0.027 (−0.175 to 0.120)	0.839	0.001 [trivial]
TF (%)	−1.183 (−3.063 to 0.696)	−2.493 (−6.723 to 1.736)	0.580	0.004 [trivial]
SBP (mmHg)	−3.970 (−5.674 to −2.266)	−0.309 (−4.149 to 3.532)	0.091	0.038 [small]
DBP (mmHg)	−4.338 (−5.689 to −2.986)	−6.269 (−9.313 to −3.224)	0.259	0.017 [small]
WC (cm)	0.784 (−0.189 to 1.758)	0.387 (−1.820 to 2.593)	0.748	0.001 [trivial]
WC-SDS	0.022 (−0.070 to 0.114)	−0.032 (−0.240 to 0.176)	0.645	0.003 [trivial]
CRP (mg/L)	−0.414 (−0.846 to 0.017)	−1.559 (−2.539 to −0.579)	*0.040*	*0.056* [*small*]
CIMT (mm)[b]	−0.001 (−0.010 to 0.008)	0.006 (−0.013 to 0.024)	0.518	0.007 [trivial]
CIMT-SDS [b]	0.011 (−0.217 to 0.238)	0.213 (−0.261 to 0.687)	0.451	0.010 [small]
FIMT (mm) [b]	−0.011 (−0.028 to 0.007)	−0.043 (−0.081 to −0.006)	0.127	0.038 [small]
FIMT-SDS [b]	0.143 (−0.111 to 0.398)	−0.217 (−0.750 to 0.317)	0.236	0.024 [small]

95%CI 95% confidence interval, *SDS* standard deviation score, *ANCOVA* analysis of covariance, *CRP* C-reactive protein, *CIMT* carotid intima-media thickness, *FIMT* femoral intima-media thickness, *TF* trunk fatness, *BMI* body mass index, *WC* waist circumference

[a] Adjusted by sex, age (baseline), trunk fatness (baseline), trunk fatness (absolute change), somatic maturation (baseline), somatic maturation (absolute change), systolic blood pressure (baseline), diastolic blood pressure (baseline), skipping breakfast (baseline), and baseline values of the dependent variable

[b] Non-sport practice is composed of 58 adolescents and Sport practice is composed of 14 adolescents

status in pediatric populations, independent of significant changes in adiposity [19].

Sex constitutes a relevant variable affecting the blood stream concentration of some inflammatory markers [21]. A cross-sectional study identified a relationship between vigorous physical activity and inflammation in boys, but not in girls [21]. In the present cohort, sex was not a significant determinant of CRP levels, probably because both were engaged in similar sports (in the analyzed sample, 80% [$n = 12$] were engaged in soccer and swimming). On the other hand, it is also necessary to take into account the reduced sample size in the Sport practice group. Therefore, our findings demonstrate that sport participation appears to be beneficial to CRP levels in boys and girls, but more research about the issue is necessary.

The significant results observed only in the FIMT could be attributed to the fact that this artery has increased oscillation in wall shear rates than other arteries [18], increasing the propensity to atherosclerotic events in this artery. In parallel, FIMT reduced in the sport group, while changes in CRP and FIMT were related to each other in the Non-sport practice group, agreeing with previous cross-sectional data [2]. The reduction in CRP levels might partly explain this finding [6], although it is important to take into account the burden of other potential confounders, such as TF and biological maturation. The significant impact of TF in the multivariate model was not a surprise as adipokines released by adipose tissue are related to insulin resistance and stimulated production of CRP by the liver [6]. Even without significant changes during the cohort, baseline measures of TF were slightly lower in the Sport practice group ($p = 0.059$) and changes in TF affected changes in FIMT, denoting the role of TF in arterial thickening in adolescents.

The independent effect of biological maturation on inflammation observed in this study is unclear in the scientific literature. The effect of biological maturation on inflammation is partially explained by its effect on adipose tissue [4]. On the other hand, the relationship between biological maturation and inflammatory markers is not completely dependent on body fatness [4], denoting the role of other pathways, such as the impact on skeletal muscle, metabolic pathways, and hormones secreted during human growth. It is noteworthy that biological maturation and regular physical exercise routines affect both skeletal muscle and growth hormones from an early age, denoting the complexity of this phenomenon.

In terms of limitation, the self-report of exercise intensity should be considered due to its lack of accuracy, mainly as our design is observational, and therefore not as controlled as a randomized clinical trial. The absence of other inflammatory markers is also relevant. This study had 12 months of follow-up, but the adolescents were engaged in these sports prior to the baseline measures, denoting that maybe more than 12 months is necessary to observe findings. Finally, the impact of the high dropout rate on our statistical power needs to be recognized. In adolescents, the effect of CRP on IMT is small [9] and the non-significant relationship between CRP and

FIMT in the Sport group needs to be analyzed with caution due to the reduced number of adolescents analyzed, which decreases the likelihood of detecting weak relationships.

In conclusion, CRP decreased in adolescents engaged in organized sports, independent of trunk fatness and biological maturation. Moreover, CRP was related to arterial thickening only in adolescents not engaged in sports. This finding denotes that sport participation seems beneficial to the control of CRP and maintenance of cardiovascular health in adolescents.

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Authors' Contributions Cayres SU conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Fabio Santos de Lira, Han C. G. Kemper, Jamile Sanches Codogno, and Maurício Fregonesi Barbosa revised the manuscript and approved the final manuscript as submitted. Fernandes RA designed the data collection instruments and coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest

Informed consent All the participants received and signed the forms prior to participation in this research.

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