C-reactive protein, physical activity and cardiorespiratory fitness in Portuguese adolescents: a cross-sectional study

Proteína C-reativa, atividade física e aptidão cardiorrespiratória em adolescentes portugueses: um estudo transversal

Proteína C-reactiva, actividad física y la aptitud cardiorrespiratoria en adolescentes portugueses: un estudio transversal

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Abstract

The goal of this study was to investigate the association of physical activity (PA) and cardiorespiratory fitness with C-reactive protein (CRP) concentration in adolescents. The sample included 386 Portuguese adolescents (n = 207, female), age 12-18 years, assessed in the year 2012. The PA was assessed with the use of accelerometers, and the cardiorespiratory fitness was assessed by the Fitnessgram Pacer test. Blood samples were collected after a 10-hour fasting, and high-sensitivity PCR concentration was further assessed. Significant associations between CRP and cardiorespiratory fitness were found for females (r = -0.313; p < 0.001) and males (r = -0.163; p < 0.05); however, when adjusted by the BMI, the associations remained significant only for females (r = -0.215; p < 0.001). Regarding the association between CRP and PA, no significant associations were found for both genders. Therefore, CRP is apparently negatively associated with cardiorespiratory fitness, with differences between males and females; for females it seems less dependent than BMI.

C-Reactive Protein; Motor Activity; Adolescent

Resumo

O objetivo deste estudo foi investigar a associação da atividade física (AF) e aptidão cardiorrespiratória com os níveis de concentração proteína C-reativa (PCR) em adolescentes. Fizeram parte da amostra 386 adolescentes Portugueses (n = 207, feminino), de 12-18 anos avaliados no ano de 2012. AF foi avaliada com acelerômetros e a aptidão cardiorrespiratória pelo teste de Vai-e-vem da bateria de testes fitnessgram. *Amostras sanguíneas foram obtidas após jejum de 10 horas e posteriormente avaliaram-se os níveis de concentração de PCR por alta sensibilidade. Foram encontradas associações significativas entre a PCR e a aptidão cardiorrespiratória no gênero feminino (r = -0,313; p < 0.001) e masculino (r = -0,163; p < 0,05), porém quando ajustadas pelo IMC essas associações permaneceram significativas apenas no gênero feminino (r = -0,215; p < 0,001). Para associações entre PCR e AF não se encontraram associações estatisticamente significativas em ambos os gêneros. Assim a PCR aparentemente se associa de forma negativa com a aptidão cardiorrespiratória, mas de forma diferenciada em função do gênero, sendo que no feminino parece menos dependente do IMC.*

Proteína C-Reativa; Atividade Motora; Adolescente

Introduction

Cardiovascular diseases (CVD) are at the top of mortality and morbidity indices in developed countries [1]. Individuals with CVD typically become symptomatic only in their adult life; however, the CVD underlying process, atherosclerosis, is often initiated in childhood, with inflammatory processes [2]. Low-grade inflammation has a pivotal role for the development of CVDs starting in childhood and adolescence [3].

C-reactive protein (CRP) is a marker of acute inflammatory process [4,5]; it is produced in the liver in response to interleukin 6 (IL-6), which, in turn, is stimulated by the tumor necrosis factor alpha (TNF-α) [5,6]. CRP is an independent cardiovascular risk fator [7], and has shown to be a powerful predictor of cardiovascular risk, even more powerful than the classic markers [8], not only in adults, but also in children and adolescents [9,10]. An investigation that compared CRP and LDL-C (Low-density lipoprotein-cholesterol) provided evidence that CRP has higher independent predictive power for future cardiovascular diseases than LDL-C [11]. In addition, associations between CRP levels and the development of type-2 diabetes mellitus [12], early arterial abnormalities in healthy young individuals of both genders [13], and adiposity [14] were also found.

Lack of physical activity (PA) in childhood and adolescence is an important risk factor for CVD [15,16]. In addition, regular PA is associated with potential benefits for health, and is considered crucial for the growth and healthy development of school-age youths [17]. A number of studies found associations between PA or cardiorespiratory fitness with CRP in adults [18,19,20]. In adolescents, however, such associations are not well established. Recently, Martinez-Gomez et al. [21], in the *HELENA Study*, investigated the combined association between PA, cardiorespiratory fitness and inflammatory markers in adolescents, and found significant associations between CRP and cardiorespiratory fitness, but not with PA measured objectively [21]. However, Owen et al. [22], in the *CHASE study*, reported a strong association between PA measured objectively and CRP in a sample of Caucasian-European, Southern-Asiatic, and Afro-Caribbean children. While some studies with young subjects find negative associations between PA or cardiorespiratory fitness and CRP [2,22,23,24,25,26,27], others do not [21,28,29,30,31,32,33,34,35,36]. Moreover, in many of these studies, the results are not presented independently from the body mass index (BMI), a potentially confounding variable of the relationship between CRP and PA or cardiorespiratory fitness [37].

Evidence is scarce and the results are confusing in relation to the association between PA and CRF with CRP in adolescentes [38,39], and previous studies in this population faced limitations due to methodology, small and heterogeneous samples, and the use of subjective PA assessment measures (such as questionnaires, for instance) [21,38]. Epidemiological studies that use questionnaires to measure PA are poorer in terms of methodology when compared with accelerometers, particularly in young populations [21,40,41]. Thus, by estimating the level of PA objectively assessed with the use of accelerometers, which provide valid and reliable results [41], this study may, perhaps, report the actual relationship between PA and CRP.

In this scenario, the goal of this study was to investigate the association between the concentration levels of CRP with PA measured objectively and CRF in Portuguese adolescents. The established premise is that the association between CRP and PA or CRF is negative for both genders.

Methods

Study design and sampling

The data of the following study were obtained from an investigation carried out by the Center for Research on Physical Activities, Health and Leisure (Centro de Investigação em Atividade Física, Saúde e Lazer – CIAFEL), University of Porto, Portugal. This study investigated a sample of adolescents enrolled in the 7th grade (primary education) and in the 10th grade (secondary education), in five schools in the North of Portugal, with age ranging from 12 to 18 years.

The participating schools had already established collaboration agreements with the University's research center, and were therefore selected for convenience, mainly for logistic and budgetary reasons.

All participants were informed about the goals of the study; they and their parents/guardians signed the informed consent form. The study was approved by School of Sports. Authorization was also given by the National Data Protection Committee (number: 12434/2011), by the Ministry of Education (number: 0246200001/2011), and by the schools' principals' office. The study was conducted in accordance with the World Medical Association Declaration of Helsinki for investigations involving human subjects.

In the course of the study, no exclusion criteria were applied to avoid discrimination. However, for this analysis, only apparently healthy adolescents were assessed, i.e., subjects with no medical diagnosis of physical or mental impairment.

Considering potential refusals to participate in the study, due to blood sample collection and the use of accelerometers, a "consent in parts" was allowed. This means that participants could consent to only some parts of the study protocol, and not to other parts. An adolescent could, for instance, be submitted to the physical fitness assessment without the use of accelerometers, or refuse to provide blood samples.

All students enrolled in the 7th and 10th grade of the participating schools were invited to take part in the study (n = 1,678). Data collection was standardized, and took place over the 2011/2012 school year; a total of 1,229 subjects took part, and 534 agreed to provide blood samples. The study was conducted by the research center (CIAFEL), and included filling out questionnaires; performing the physical fitness assessment battery tests (Fitnessgram and Alpha); objective assessment of physical activity (accelerometry); assessment of anthropometric measures; blood pressure measurement, and blood sample analysis. The participants were evaluated during physical education classes by physical education teachers specifically trained for data collection (anthropometric measures, batteries of physical fitness tests, physical activity, questionnaire completion, and blood pressure measurement). Blood samples were collected by nurses who went to the schools for that purpose.

For the present study, a subsample of 386 adolescents (207 females) with all (100%) the information about PA, cardiorespiratory fitness and CRP was considered.

Instruments and variables

- **Anthropometry**

a) Height

Height was measured with the use of a stadiometer (Seca 213, Seca Medical Scales and Measuring Systems, UK), with accuracy in millimeters. Measurements were taken in the anthropometric position, with subjects in bare feet or wearing socks. After placing the subjects in the proper position, the horizontal plastic rod was moved until it reached the vertex, and the figure in centimeters of the height was recorded.

b) Weight

Weight was measured with the adolescents wearing only t-shirts and shorts, on a portable electronic scale (Tanita BF 350, Tanita Corp., Arlington Heights, U.S.A.); later, the body mass index (BMI) was calculated as weight/height^2, and expressed as kg/m^2.

- **Sexual maturity status**

To establish the sexual maturity status (ranging from 1 to 5), each subject was asked to self-assess their secondary sexual characteristics. Breast development stage, for girls, and genital development, for boys, were assessed according to the criteria established by Tanner & Whitehouse [42].

- **Objective measures of physical activity**

The PA standards were objectively assessed with the use of accelerometers Actigraph GT1-M (Actigraph, Pensacola, U.S.A.). The subjects of the study used the accelerometer for 7 consecutive days (5 week day and 2 weekend days). The subjects were instructed to use the accelerometer at their waist throughout the day, and to remove them only during water activities and to sleep. The epoch length was 2 seconds. For this study, only participants with valid accelerometry data (at least 3 days, with 10 hours or more of monitored data) were included in the analysis. For this study, the proportion of time was split into moderate, vigorous and very vigorous PA in accordance with the cutoff points established by Freedson (1998, apud Trost et al.) [43].

- **Assessment of the cardiorespiratory fitness**

To assess the cardiorespiratory fitness, the 20-meter Pacer test was used [44]. This test predicts the maximum cardiorespiratory capacity, and provides significant associative evidences so that it can be used to assess cardiorespiratory fitness in children and adolescentes [45]. For this test, the participants have to run between two lines set 20 meters apart, and must run in synchronization with signal beeps. The initial speed at the initiation of the test is 8.5km/h which is gradually increased by 0.5km/h increments at each minute, reaching 18km/h at minute 20. A signal beep would mark each increment. The participants were asked to keep the pace until exhaustion. The test finished when the participant failed to reach the line at the end concurrently with the beep for two consecutive times. Otherwise, the test finished when the participant stopped due to fatigue. The participants were encouraged by the investigators to perform as best as they could, and to keep on in the test for as long as possible. The total number of laps of each participant was recorded. Later, the Vo_{2max} of each participant was calculated by the equation of Léger et al. [44].

- **Measures of high-sensitivity CRP**

All blood samples were collected from participants who were fasting for at least 10 hours, early in the morning. Blood sample was collected from a vein at the antecubital fossa, with the subjects in a sitting position. For that purpose, vacuum tubes manufactured by Sarstedt (Sarsdedt Ag & Co, Nümbrecht, Germany), with gel barrier to separate serum form the blood clot. After rest at room temperature for about 30 minutes, the samples were centrifuged for 10 minutes at 3000 rot/min for serum to be obtained. The high-sensitivity CRP levels were measured by latex-enhanced immunoturbidimetric assay using Siemens Advia 1600/1800 (Siemens AG, Erlangen, Germany).

- **Statistical analyses**

For the data statistical analyses, the software IBM-SPSS (IBM Corp., Armonk, U.S.A.) version 20.0 for Windows, was used, with 95% confidence level (95%CI) and 5% significance level ($p < 0.05$). Gender differences were established by the t test for independent samples. CRP levels were normalized with the use of natural logarithm, as they did not present normal distribution. For each gender, partial correlations were made (Pearson's correlation coefficient) to check the association between CRP with the cardiorespiratory fitness and PA variables adjusted for age, sexual maturity and BMI. To calculate the power of the sample, the software G*Power 3.1.9.2 (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3) (was used, and post-hoc power calculation was made separately for genders ($p < 0.05$) and established for each significant correlation in the models used. For females, the results were 0.99 and 0.88 for correlation models 1 and 2, respectively; for males, 0.61 for model 1.

Results

The descriptive characteristics of this study and gender differences are presented in Table 1. The mean CRP values in Table 1 are presented in mg/L and not normalized. No significant differences were seen between CRP concentration for male (0.90 ± 1.55) and female (0.68 ± 1.40) adolescents. There were significant differences between genders for weight, height and Vo_{2max} ($p < 0.005$ for all).

Significant partial correlations were found between cardiorespiratory fitness and CRP for both females ($r = -0.313$; $p = 0.00$) and males ($r = -0.163$; $p = 0.02$) when adjusted for age and sexual maturity, as presented in Table 2. However, when BMI is included as a control variable, this association remained significant for females only ($r = -0.215$; $p = 0.00$). No significant association was found for the PA measured objectively.

Discussion

Low-grade inflammation seems to play an important role in the development of CVD starting in childhood and adolescence [13]. Over the past decade, a number of scientific investigations were conducted that provided enough evidence showing the power of CRP as predictive of CVD [18].

There are CRP concentration cutoff points that represent the CVD risk for adults: < 1.0mg/L (low risk), 1.0 until 3.0mg/L (intermediate risk), and > 3.0mg/L (high risk) [46]. However, for children and adolescents no such scale exists. In a study with 1,617 Finnish children and adolescents, age 3 to 18 years, assessed in 1980 and reassessed in 2001 for high-sensitivity CRP, no significant association was found between CRP concentration in childhood and in adult life [47]. In our sample, we found 42 children and adolescents that had CRP concentration higher than 3.0mg/L. Cross-sectional studies are necessary to determine the meaning of these concentration levels in children and adolescents.

In this study, despite CRP concentration differences between genders, these differences are not statistically significant. The results we found are in accordance with those found in some studies [21,30,48], but are contrary to those of other studies [9,14]. For Thomas et al. [30], due to the great CRP concentration variation in children and adolescents, and the small sample of the studies, it is unlikely that gender differences may be explained. Large-scale epidemiological studies are clearly necessary to fully clarify the role of gender in CRP concentration, in these populations.

Significant associations between CRP and BMI were also found in both genders (preliminary data not shown), which is in accordance with other studies [24,25,29,30,32]. The current literature shows body fat as the main influencing factor of CRP concentration [37]. Cook et al. [9], in 2000, were the first to demonstrate the close relationship between CRP and body fat in a sample of 699 children age 10 and 11 years [9], which was further confirmed in the *NHANES III* study with 3,512 children and adolescents age between 8 and 16 years [49]. Thus, due to the close relationship found between BMI and CRP in this and in other studies, BMI was also used as an adjusted variable in the association of PA and cardiorespiratory fitness with CRP.

Table 1

Characteristics of the sample under study.

Characteristics	Mean (± standard deviation)		
		Gender	
	Total sample (n = 386)	Male (n = 179)	Female (n = 386)
Age (years)	14.03 (±1.64)	13.93 (±1.61)	14.13 (±1.66)
Weight (kg)	53.88 (±12.43)	54.50 (±12.71)	53.33 (±12.24) *
Height (cm)	159.18 (±9.05)	160.59 (±10.76)	158.02 (±7.05) *
BMI (kg/m2)	21.13 (±3.89)	20.97 (±3.75)	21.26 (±4.04)
Sexual maturity status (%)			
I	0.65	1.21	0.00
II	16.00	13.02	4.31
III	22.24	41.39	26.50
IV	47.55	32.68	55.65
V	13.61	11.70	13.54
PCR (mg/L)	0.93 (±1.85)	0.90 (±1.55)	0.68 (±1,40)
$Vo2_{máxima.}$	41.88 (±6.63)	45.57 (±6.60)	38.71 (±4.75) *
Moderate, vigorous and very vigorous PA	8.60 (±4.60)	10.49 (±4.99)	7.03 (±2.97) *

BMI: body mass index; CRP: C-reactive protein; PA: physical activity.

* Significantly different from males (t test for independent samples).

Table 2

Partial correlations between C-reactive protein (CRP) cardiorespiratory fitness and physical activity (PA).

CRP (mg/L) *	Cardiorespiratory fitness (Vo_{2max})	Moderate, vigorous and very vigorous PA (%)
Model 1		
Females	-0.313 **	-0.032
Males	-0.163 ***	-0.019
Model 2		
Females	-0.215 **	0.008
Males	-0.039	-0.190

Model 1: adjusted for age and sexual maturity; Model 2: adjusted for age, sexual maturity and body mass index;

* Values transformed into natural log;

** p value < 0.001;

*** p value < 0.05.

This study found significant partial correlations between CRP and cardiorespiratory fitness for both genders, adjusted for age and sexual maturity; however, when BMI was included as a variable for adjustment, these associations were no longer significant for males, but only for females. This may perhaps be explained by the difference in Vo_{2max} found between both genders. In the *HELENA Study*, conducted in ten European countries with adolescents age 12.5 to 17.5 years [21], a negative association was found between CRP and cardiorespiratory fitness (β = 0.188; $p < 0.001$) adjusted for age, gender and city; when BMI was included as a variable of adjustment, the values decreased, but still remained significant (β = -0.124; $p < 0.011$). Kwon and collaborators, in the *2010 NHANES* study with 3,202 youths, age 12 to 19 years, found CRP concentration levels significantly higher in subjects who presented low cardiorespiratory fitness [25]. However, in a study with 416 Spanish adolescents, age 13 to 18.5 years, with samples adjusted for gender, sexual maturity and body fat, no significant association was found between CRP and cardiorespiratory fitness [36].

In most studies that investigated the same variables examined in this one, the results are not presented according to gender. Tam et al. [37] reinforce that potential CRP-related influences could be observed were the results disaggregated according to gender. In the model presented in this study, in addition to possible confounding variables, such as age, sexual maturity status and BMI, the results were analyzed by gender, based on the theoretical assumption of the possible association between body fat and CRP concentration, and hormonal differences between genders, as suggested by Kwon [50].

The association between PA and CRP in youths has been examined particularly with the use of questionnaires; indeed, studies that use objective assessment of PA are limited [38]. Data collected from adolescents by means of questionnaires are poorer methodologically when compared with objective measures obtained with the use of accelerometers [21]. In this study, we have observed the association between CRP and the proportion of moderate, strenuous and very strenuous PA. Our results did not find significant association between CRP and the proportion of moderate, strenuous and very strenuous PA adjusted for age, sexual maturity and BMI. These findings are consistent with those reported in the *NHANES study*, with 1,643 children and adolescents, age 6 to 17 years, in which no association was found between CRP and PA measured objectively [34]. Similarly, in two other recent studies, no association was found between PA measured objectively and CRP [21,32]. However, Parrett et al. [24] explored a joint association between body fat, CRP and PA (measured by pedometers) and found a negative association ($r = -0.49$, $p < 0.05$) in a group of 44 children.

It is possible that childhood and adolescence is too early for one to observe a direct and independent relationship between PA and CRP concentration [30]. It is possible that when CRP concentration is normal, PA may have little influence [34]. However, there is no CRP reference value established for children and adolescents, which may lead these results to be re-assessed.

One of the strengths of the study was that it investigated the association between CRP concentration and objective measures of PA, and observed the assessments independently from the BMI, and disaggregated by gender. Our results should be interpreted taking into consideration some limitations. First, one must acknowledge the cross-sectional nature of the study, and because of that no causal directionality could be inferred. Another important factor to be observed is the 0.61 power of the sample for males. Longitudinal and intervention studies may provide a different perspective, and perhaps present more robust results regarding the association between CRP with PA and cardiorespiratory fitness in adolescents.

The results of this study, therefore, suggest that CRP is negatively associated with cardiorespiratory fitness, but with gender-related differences: it seems less dependent on BMI in females. Thus, more studies with representative samples are necessary to clarify the relationship between PA and cardiorespiratory fitness with CRP concentration in children and adolescents, as well as longitudinal epidemiological studies.

Resumen

El objetivo de este estudio fue investigar la asociación entre la actividad física (AF) y la aptitud cardiorrespiratoria con niveles de concentración de proteína C-reactiva (PCR) en adolescentes. La muestra estuvo conformada por 386 adolescentes portugueses (n = 207, femenino), de 12-18 años, evaluados en el año 2012. La AF se evaluó mediante acelerómetros y la aptitud cardiorrespiratoria se evaluó por el test de Leger de 20 metros. Las muestras de sangre se obtuvieron después de 10 horas de ayuno, y luego se evaluaron los niveles de concentración de PCR de alta sensibilidad. Se encontraron asociaciones significativas entre la PCR y aptitud cardiorrespiratoria en el género femenino (r = -0,313; p < 0,001) y masculino (r = -0,163; p < 0,05), pero cuando se ajustan por el IMC estas asociaciones se mantuvieron sólo significativas en el género femenino (r = -0,215; p < 0,001). Para las asociaciones entre la PCR y la AF no mostraron una asociación estadísticamente significativa en ambos géneros. Así, aparentemente la PCR se asoció negativamente con la aptitud cardiorrespiratoria, pero de manera diferente según el género, siendo que en el femenino parece ser menos dependiente del IMC.

Proteína C-Reactiva; Actividad Motora; Adolescente

Contributors

C. A. Agostinis Sobrinho participated design, writing and approval of the final version. C. M. M. Moreira collaborated in writing and treatment of data. J. A. P. Silva Mota participated in a correction, writing and development. R. M. R. Santos pasrticipated in a writing, correction and approval of the final version.

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