Self-initiated physical activity is associated with high sensitivity C-reactive protein: A longitudinal study in 5,030 adults

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ABSTRACT

Background and aims: Structured regular exercise programs decrease high-sensitivity C-reactive protein (hsCRP), a marker of low-grade inflammation in adults. Longitudinal effects of self-initiated physical activity levels (PAL) on hsCRP are less clear. This study evaluated the association of longitudinal changes in hsCRP in relation to modifications in PAL, over time, in a large sample of adults.
Methods: Participants included 5030 adults, 4045 (80%) males, undergoing routine health screening examinations. Elevated level of hsCRP was defined as $\geq$3 mg/L. Self-reported PAL, height, weight, blood pressure and blood samples were collected at baseline and after a median of 2.9 years (P25th 1.97 and P75th 4.37 yrs). Participants were stratified according to their PAL at baseline and follow-up as: i) persistently physically inactive; ii) became physically inactive; iii) became physically active; iv) persistently physically active (active both at baseline and follow-up).
Results: Persistently physically active participants had lower odds of having higher hsCRP (OR = 0.35 [95% CI: 0.25 to 0.48]). The maintenance of high PAL was associated with lower hsCRP in both sexes (men: OR = 0.44 [0.30 to 0.65] and women: OR = 0.35 [0.16 to 0.76]). Participants with overweight/obesity (OR = 0.43 [95% CI: 0.29 to 0.63]) and smokers (OR = 0.123 [95% CI: 0.03 to 0.60]) who were persistently active had lower odds of having higher hsCRP compared to physically inactive peers.
Conclusions: Self-initiated PAL was longitudinally associated with hsCRP in adults. The data suggest that the initiation or maintenance of PA attenuates the low-grade inflammatory state, independent of sex, body weight and smoking status.

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1. Introduction

Low-grade inflammation plays an important role in all stages of atherosclerotic cardiovascular disease and is associated with an increased risk of cardiovascular morbidity and mortality. C-reactive protein (hsCRP) is a non-specific marker of inflammation and is an independent biomarker of higher cardiovascular risk [1] and early mortality in adults [2]. Recently, the Canakinumab

Antiinflammatory Thrombosis Outcome Study (CANTOS) trial showed that reduction in inflammation by a monoclonal antibody against interleukin 1-beta, and assessed by lowering of plasma hsCRP concentrations, was associated with lower rates of recurrent cardiovascular events, independent of LDL cholesterol levels [3].

Previous studies have shown that structured regular exercise programs decrease the circulating levels of various inflammatory biomarkers including hsCRP in adults and the elderly [4–6]. However, these exercise programs were usually of short duration and typically performed in research settings. Effective implementation of these intervention programs in real-life public health conditions is challenging. Previously we have demonstrated that

self-reported changes in physical activity levels (PAL) were associated with improvements in several health parameters [7—9]. However, the potential longitudinal effect of unstructured and self-initiated PAL, in free-living conditions, on residual hsCRP is unknown. Therefore, given the importance of hsCRP as a marker of higher cardiovascular risk, would be interesting to investigate whether individuals who maintain or increase their PAL present lower values of hsCRP in a longitudinal design study. Thus, the aim of this study was to identify the modifications in PAL over time and changes in hsCRP values in a large sample of adults asymptomatic for cardiovascular disease.

2. Materials and methods

2.1. Study design

We included all consecutive adults between 18 and 60 years of age, who participated in an employer-sponsored routine health evaluation at the Preventive Medicine Center of the Hospital Israelita Albert Einstein (Sao Paulo, Brazil) from January 2007 to December 2013. In this survey were considered only participants who returned for a follow-up visit at least one year after the initial encounter (for participants with multiple return visits, the last visit was used as the follow-up). All participants were invited to voluntarily participate in a health promotion program. We analyzed hsCRP levels and PAL at baseline and during a follow-up visit that occurred between 12 and 82 months after the initial encounter. The present study was approved by our institutional review board, and a consent form was waived.

Initially, the dataset consisted of 7741 individuals of both sexes who had baseline and follow-up data. To avoid misclassification of hsCRP values due to potential influence of acute inflammation, participants who had hsCPR levels ≥ 10 mg/L in any of the moments were excluded ($n = 311$). Additionally, considering all variables involved in this study, individuals with any missing data ($n = 2169$) and less than 12 months of follow-up ($n = 231$) were also excluded. Therefore, the final sample involved in this study was composed of 5030 adults (4045 men) that presented the complete data at baseline and follow-up.

Measurement of hsCRP was performed at baseline and follow-up visits. Blood samples were collected after an overnight fast and analyzed as part of the routine clinical workflow. Laboratory analyses included determination of hemoglobin concentrations, a standard lipid panel and fasting glucose using a Vitros platform automated laboratory system (Johnson & Johnson Clinical Diagnostics, New Brunswick). The laboratory responsible for all blood analyses meets the standardized criteria for quality control adopted by the Brazilian Health Ministry. Measurement of hsCRP (expressed in mg/L) was performed by a turbidimetric method on a nephelometry system (Dade-Boehring, EUA).

PAL was assessed by the short version of International Physical Activity Questionnaire (IPAQ-SF) which was previously validated in a similar population [10]. The participants fulfilled the questionnaire under supervision of a trained staff member. At baseline, participants were classified according to the IPAQ-SF into one of two distinct qualitative categories of PA: physically active (≥ 150 min/week of moderate-to-vigorous intensity) or inactive (<150 min/week of moderate-to-vigorous intensity). Considering both baseline and follow-up, participants were classified into three categories: i) persistently physically inactive (inactive both at baseline and follow-up); ii) physically active in one time point (active at baseline or at follow-up); iii) persistently physically active (active both at baseline and follow-up).

Anthropometric assessments included measurement of body mass in kg and height in meters (m). Body mass index (BMI

[expressed as kg/m^2]) was defined as the individual's weight (kg) divided by the square of their height (m^2). Overweight/obesity was determined as BMI ≥ 25 kg/m^2.

Blood pressure was measured in triplicate, in the seated position, according to the standard method recommended by the American Heart Association [11] after the participants had rested for at least 5 min. The measurements were performed in both upper limbs using the auscultatory method with an aneroid sphygmomanometer, and employing phases I and V of the Korotkoff sounds.

Medical records were accessed in order to identify the prescription of statins, as well as the previous diagnoses of arterial hypertension, dyslipidemia and diabetes mellitus. Alcohol consumption was assessed through face-to-face interview using the Alcohol Use Disorders Identification Test (AUDIT) [12].

2.2. Statistical analysis

Descriptive statistics for continuous variables were expressed as means and standard deviations, except for hs-CRP expressed in median and interquartile range. Categorical variables were presented as rates and their 95% confidence intervals (95% CI).

Baseline values of age, sex, blood glucose, hemoglobin, statin use, alcohol consumption (AUDIT), systolic and diastolic blood pressure (SBP and DBP, respectively) were used as covariates in the multivariate models. The time of follow-up was stratified into 1.0—1.9 years, 2.0—2.9 years and ≥ 3 years. Independent variables were measured at two-time points (baseline and follow-up) and thus variables with longitudinal approach were created. For overweight/obesity three categories were created: BMI ≥ 25 kg/m^2 in none, BMI ≥ 25 kg/m^2 in just either baseline or follow-up and BMI ≥ 25 kg/m^2 in both baseline and follow-up visits. For smoking three categories were created: non-smoker in both visits, current smoker in just either baseline or follow-up and current smoker in both baseline and follow-up. Considering each disease diagnosed by the attending physician (hypertension, dyslipidemia and diabetes mellitus) three categories were created: positive diagnosis in none, positive diagnosis in just either baseline or follow-up and positive diagnosis in both baseline and follow-up. The comparison of sample characteristics among these groups was performed by ANOVA one-way, except for hs-CRP in which was used Kruskal-Wallis test.

A hsCRP value of ≥ 3 mg/L was defined as "higher hsCRP" [13]. The main outcome of this study was higher hsCRP in both baseline and follow-up. The impact of physical activity on hsCRP levels was estimated by binary logistic regression, which was expressed as odds ratios (OR) and 95% CI. Multivariate models were developed adjusting for age, sex, arterial hypertension, dyslipidemia, diabetes mellitus, time of follow-up, smoking status, overweight/obesity, blood pressure, glucose, statin use, hemoglobin values and alcohol consumption (AUDIT). All statistical analyses were performed in the software BioEstat (release 5.0) and statistical significance (p-value) was set at 0.05.

3. Results

Table 1 shows clinical and laboratory characteristics of study participants. Mean age was 41.3 ± 8.5 and there was a higher proportion of men (p-value = 0.002). The median follow-up time was 2.9 years (P25th 1.97 and P75th 4.37), the medians (P25th and P75th) for hsCRP were 1.1 (0.5 and 2.1) and 1.0 (0.5 and 2.0) at baseline and follow-up, respectively. The prevalence of higher hsCRP was similar over time (baseline: 14.8% and follow-up: 15.5%; $p = 0.263$), while high levels of hsCRP at both baseline and follow-up were encountered in 6.5% (95% CI: 5.8 to 7.2) of the entire sample.

Table 2 shows sample characteristics according to PAL groups.

Table 1
General characteristics of the studied population ($n = 5030$).

Variable	Categories	Descriptive statistics n (%)
Sex		
	Male	4045 (80.4)
	Female	985 (19.6)
Age baseline		
	<30 years	366 (7.3)
	30-39 years	2018 (40.1)
	40-49 years	1847 (36.7)
	≥50 years	799 (15.9)
Time of follow-up		
	1.0−1.9 years	1330 (26.4)
	2.0−2.9 years	1338 (26.6)
	≥3 years	2362 (47.0)
Body mass index ≥25 kg/m^2		
	None	1669 (33.2)
	Either baseline or follow-up	607 (12.1)
	Both	2754 (54.7)
Hypertension diagnosis (yes)		
	None	4229 (84.1)
	Only at follow-up	267 (5.3)
	Both	534 (10.6)
Diabetes diagnosis (yes)		
	None	4882 (97.1)
	Only at follow-up	45 (0.9)
	Both	103 (2.0)
Dyslipidemia diagnosis (yes)		
	None	2096 (41.7)
	Only at follow-up	1428 (28.4)
	Both	1506 (29.9)
Statin use		
	None	4108 (81.7)
	Either baseline or follow-up	573 (11.4)
	Both	349 (6.9)
Smoking (yes)		
	None	4453 (88.5)
	Either baseline or follow-up	298 (5.9)
	Both	279 (5.5)
C-reactive protein (≥3 mg/L)		
	None	3833 (76.2)
	Either at baseline or follow-up	870 (17.3)
	Both	327 (6.5)

Table 3
Parameters associated with high hsCRP levels in study participants at baseline and follow-up ($n = 5030$).

Variable	Categories	High hsCRP[a] n (%)	p
Sex	Male	241 (6.0)	0.002
	Female	86 (8.7)	
Age baseline	<30 years	33 (9.0)	0.223
	30-39 years	107 (5.3)	
	40-49 years	123 (6.7)	
	≥50 years	64 (8.0)	
Time of follow-up	1.0-1.9 year	108 (8.1)	0.023
	2.0-2.9 years	77 (5.8)	
	≥3 years	142 (6.0)	
BMI ≥25 kg/m^2	None	51 (3.1)	0.001
	Either baseline or follow-up	25 (4.1)	
	Both	251 (9.1)	
Hypertension diagnosis	None	259 (6.1)	0.0002
	Only follow-up	14 (5.2)	
	Both	54 (10.1)	
DM diagnosis	None	311 (6.4)	0.025
	Only follow-up	4 (8.9)	
	Both	12 (11.7)	
DLP diagnosis	None	122 (5.8)	0.210
	Only follow-up	103 (7.2)	
	Both	12 (11.7)	
Statin use	None	274 (6.7)	0.097
	Either baseline or follow-up	40 (7.0)	
	Both	13 (3.7)	
Smoking (yes)	None	269 (6.0)	0.001
	Either baseline or follow-up	23 (7.7)	
	Both	35 (12.5)	
Physically active	None	182 (9.0)	0.001
	Either baseline or follow-up	100 (6.1)	
	Both	45 (3.3)	

BMI = body mass index; AH = arterial hypertension; DM = diabetes mellitus; DLP = dyslipidemia.
[a] C-reactive protein ≥3 mg/L in both (baseline and follow-up).

were associated with female sex ($p = 0.002$), with shorter follow-up time ($p = 0.023$), overweight/obesity ($p = 0.001$), hypertension ($p = 0.002$) and diabetes at baseline ($p = 0.025$), and smoking ($p = 0.001$).

In the overall sample, 27% of participants were active at both time-points, 40.2% sedentary at both time-points, 20.7% became active from baseline to follow-up and 12.1% became sedentary from baseline to follow-up.

Persistently physically active participants both at baseline and follow-up had lower prevalence of higher hsCRP than persistently physically inactive counterparts (Active: 3.3% vs. Inactive: 9.0%; $p = 0.001$).

Table 4 shows the multivariate adjusted prevalence of higher hsCRP at baseline and follow-up. The maintenance of high PAL

Subjects physically active in both baseline and follow-up were older, presented a higher proportion of men, a lower proportion of smokers and diabetics, had lower BMI and hs-CRP concentrations ($p < 0.05$). Subjects that were physically active in one time point had lower hs-CRP concentrations and lower proportion of diabetics compared to the group that was not physically active at any time point ($p < 0.05$).

Table 3 shows univariate clinical associations with higher hsCRP at baseline and follow-up. In both assessments, higher hsCRP values

Table 2
Characteristics of the sample according to physical activity pattern ($n = 5030$).

	Physically active (considering baseline and follow-up)			
	None (n = 2021)	Either baseline or follow-up (n = 1656)	Both (n = 1358)	p
Sex (% men)	76.9	82.3[b]	83.4[b]	<0.01
Age (years)	40.8 (8.2)	40.9 (8.6)	42.7 (8.8)[b c]	<0.01
C-reactive protein (mg/L)[a]	1.20 (1.80)	1.10 (1.50)[b]	0.90 (1.30)[b]	<0.01
Body mass index (kg/m^2)	26.4 (4.1)	26.2 (3.7)	25.6 (3.3)[b c]	<0.01
Smoking (%)	10.5	9.1	7.8[b]	0.03
Hypertension (%)	10.9	10.1	10.8	0.71
Diabetes (%)	2.8	1.6[b]	1.5[b]	0.01
Dyslipidemia (%)	29.0	30.9	30.2	0.44

[a] Expressed as median (interquartile range).
[b] Significantly different from none group.
[c] Significantly different from Either baseline or follow-up group.

Table 4

Multivariate association of high hsCRP by physical activity level according to sex, age and time of follow-up ($n = 5030$).

Variables	Physically active (considering baseline and follow-up)		
	None	Either baseline or follow-up	Both
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex[a]			
Male (n = 4045)	1.00 (reference)	**0.677 (0.497 to 0.921)**	**0.429 (0.290 to 0.633)**
Female (n = 985)	1.00 (reference)	0.981 (0.586–1.643)	**0.403 (0.183 to 0.884)**
Age baseline[b]			
<30 years (n = 366)	1.00 (reference)	1.323 (0.541–3.231)	0.231 (0.043–1.234)
30-39 years (n = 2018)	1.00 (reference)	0.793 (0.508–1.238)	**0.541 (0.298 to 0.981)**
40-49 years (n = 1847)	1.00 (reference)	**0.579 (0.366 to 0.917)**	**0.390 (0.224 to 0.680)**
≥50 years (n = 799)	1.00 (reference)	0.606 (0.309–1.188)	**0.334 (0.152 to 0.739)**
Time of follow-up[c]			
1.0–1.9 year (n = 1330)	1.00 (reference)	1.022 (0.641–1.629)	0.611 (0.351–1.066)
2.0–2.9 years (n = 1338)	1.00 (reference)	0.798 (0.473–1.345)	**0.234 (0.091 to 0.605)**
≥3 years (n = 2362)	1.00 (reference)	**0.537 (0.354 to 0.815)**	**0.389 (0.229 to 0.661)**

OR = odds ratio; 95% CI = 95% confidence interval.

[a] Adjusted by age (baseline), time of follow-up, body mass index (baseline), smoking, systolic blood pressure (baseline), diastolic blood pressure (baseline), glucose (baseline), diagnosis of arterial hypertension, diabetes mellitus, dyslipidemia, statin use, hemoglobin values and alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]).

[b] Adjusted by sex, time of follow-up, body mass index (baseline), smoking, systolic blood pressure (baseline), diastolic blood pressure (baseline), glucose (baseline), diagnosis of arterial hypertension, diabetes mellitus, dyslipidemia, statin use, hemoglobin values and alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]).

[c] Adjusted by age (baseline), sex, body mass index (baseline), smoking, systolic blood pressure (baseline), diastolic blood pressure (baseline), glucose (baseline), diagnosis of arterial hypertension, diabetes mellitus, dyslipidemia, statin use, hemoglobin values and alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]).

(both at baseline and follow-up) was associated with lower hsCRP values in both sexes (57% and 60% lower OR for men and women respectively). These associations were also observed across age groups, as well as in individuals with longer time of follow-up.

Table 5 shows the multivariate association of PAL with excess body weight and smoking status. Individuals who maintained high PAL with normal body mass index (<25 kg/m^2) had 71% less odds of having higher hsCRP (OR = 0.292 [95% CI: 0.110 to 0.774]), while physically active overweight/obese individuals had 57% less chance to have higher hsCRP (OR = 0.423 [95% CI: 0.284 to 0.630]).

4. Discussion

The main findings of the current study were: (i) physically active individuals (physically active at baseline and follow-up) had lower likelihood of having higher hsCRP; (ii) the maintenance of high PAL was associated with lower odds of higher hsCRP independent of sex, body mass index and smoking status; (iii) individuals who maintained PAL had decreased hsCRP values during the follow-up period (iv) longer maintenance of PAL was associated with greater decrease in hsCRP values.

Relatively small cross-sectional studies have shown an inverse relationship between PAL and hsCRP [14]. The results of the present study confirmed such a relationship between PAL and hsCRP, longitudinally, in a large sample. Interestingly, the association between PAL and hsCRP persisted after adjustment for BMI, which is closely associated with low-grade inflammation [15]. In addition, overweight and obese participants who maintained high PAL had 57.7% lower chances of having high levels of hsCRP, despite the changes in their BMI. Therefore, our results reinforce the important role that daily maintenance of PAL plays in the improvement of low-grade inflammation in adults with varied weight status.

In the current study, we demonstrated that the maintenance of PAL had a favorable impact on hsCRP values in both men and women, confirming the anti-inflammatory and cardio-protective effects of physical activity in both sexes. This observation is important because women are less physically active than men across their life span [16], presenting an increased risk of development of cardiovascular and metabolic diseases, particularly after menopause [17,18]. Interestingly, the impact of higher PAL on hsCRP values was more consistent with longer duration of follow-up visits, signifying the role of sustained maintenance of regular PAL

Table 5

Multivariate association between high hsCRP and physical activity levels according to excess body weight and smoking status ($n = 5030$).

Variables	Physically active (taking into account baseline and follow-up)		
	None	Either baseline or follow-up	Both
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Body mass index ≥25 kg/m^{2a}			
None (n = 1669)	1.00 (reference)	0.671 (0.350–1.286)	**0.292 (0.110 to 0.774)**
Either baseline or follow-up (n = 607)	1.00 (reference)	2.190 (0.777–6.175)	1.195 (0.349–4.088)
Both (n = 2754)	1.00 (reference)	**0.690 (0.508 to 0.938)**	**0.423 (0.284 to 0.630)**
Smoking (yes)[b]			
None (n = 4453)	1.00 (reference)	**0.693 (0.518 to 0.927)**	**0.437 (0.300 to 0.637)**
Either baseline or follow-up (n = 298)	1.00 (reference)	1.481 (0.462–4.753)	0.938 (0.228–3.857)
Both (n = 279)	1.00 (reference)	1.120 (0.445–2.818)	**0.113 (0.023 to 0.569)**

OR = odds ratio; 95% CI = 95% confidence interval.

[a] Adjusted by sex, age (baseline), time of follow-up, smoking, systolic blood pressure (baseline), diastolic blood pressure (baseline), glucose (baseline), diagnosis of arterial hypertension, diabetes mellitus, dyslipidemia, statin use, hemoglobin values and alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]).

[b] Adjusted by sex, age (baseline), time of follow-up, body mass index (baseline), systolic blood pressure (baseline), diastolic blood pressure (baseline), glucose (baseline), diagnosis of arterial hypertension, diabetes mellitus, dyslipidemia, statin use, hemoglobin values and alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT]).

over longer periods for clinically relevant improvements in hsCRP values.

Maintenance of PAL was also associated with improvements in hsCRP values in all age categories, except for adults younger than 30 years-old. Loprizi et al. [19] in a large cross-sectional survey have also identified a negative relationship between objectively measured PAL and hsCRP values in adults ($\geq$20 years-old), but not in adolescents ($\leq$19 years-old). The underlying mechanisms, that explain this protective effect of PAL on low-grade inflammation only in subjects aged >30 years, are not clear. However, the progressive nature of cardiovascular risk including chronic low-grade inflammation may play a role, as in older ages the prevalence of these risk factors is higher.

The mechanisms that explain how PAL reduces inflammation and suppresses hsCRP values are not well defined. Acutely, contracting skeletal muscle produces and secretes several cytokines (myokines), most notably IL-6, which mediates metabolic changes during exercise [20]. IL-6 release from muscle increases up to 100-fold during contractile exercise and its production results in increased systemic anti-inflammatory cytokines. Thus, it is possible that several expositions to exercise could lead to lower basal levels of circulating inflammatory markers, as well as reduce the inflammatory response to acute exercise. Moreover, other mechanism such as a decrease in cytokine production by adipose tissue, improvement in insulin sensitivity and improvement on endothelial function may lead lower levels of circulating inflammatory markers.

Limitations of this study should be recognized. The use of self-reported questionnaires to assess PAL, as opposed to more sophisticated objective approaches, is a limitation. However, notably, it has been previously demonstrated that the use of validated questionnaires from participants in their free-living conditions produced results similar to those when PAL was objectively measured [19]. In addition, despite the behavioral nature of physical activity, a reverse causality of inflammation causing inactivity cannot be discarded. Our study is also limited by the lack of information on the dose-response effect of PAL, thus precluding us from knowing the minimum threshold of PAL that is necessary to maintain optimum levels of hsCRP. The absence of more accurate measures of adiposity and other biochemical variables such as creatinine and uric acid limits additional interpretations that could have shed light on mechanisms. The number of participants with <30yrs of age was relatively low and the potential influence of this limitation in the interpretation of the results cannot be discarded. Finally, we did not have data on menopausal status in women, which could be a potential confounding factor, as well.

In conclusion, the current study suggests that, in adults, the initiation of physical activity and the maintenance PAL play important roles in the attenuation of hsCRP levels, independently of sex, body weight and smoking status. The relationship between PAL and low-grade inflammation and the crucial role of maintenance of PAL in the reduction of hsCRP have profound clinical implications in the planning of preventive intervention strategies and physical activity-based education programs aimed at reducing the risk of atherosclerotic cardiovascular disease.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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