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Inflammatory effects of high and moderate intensity exercise - a Systematic Review

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Versão final após defesa

Dissertação para obtenção do grau de mestre em

Medicina

(ciclo de estudos integrado)

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Abstract

Background: Exercise leads to a robust inflammatory response mainly characterized by the mobilization of leukocytes and an increase in circulating inflammatory mediators produced by immune cells and directly from the active muscle tissue. Both positive and negative effects on immune function and susceptibility to minor illnesses were observed. While engaging in moderate activity may enhance immune function above sedentary levels, excessive amounts of prolonged, high-intensity exercise may impair immune function. The goal of this systematic review was to clarify the inflammatory effects in response to different exercise intensities.

Methods: A systemic search examining exercise and inflammation was performed on PubMed and completed on July 31st, 2017. Eighteen articles were included, and their quality was assessed. The specific components that were examined included circulating blood levels of cytokines, leukocytes, creatine kinase (CK) and C-reactive protein (CRP).

Results: Most of the intervention studies showed changes in the assessed biomarkers, although these changes were not always consistent. White blood cells (WBC) had an increase immediately after intensive exercise (> 64 % VO_{2max}), without alteration after moderate exercise (46 - 64% VO_{2max}). The results suggested an elevation of the pro-inflammatory cytokines, namely IL-6, followed by an elevation of IL-10 that were more evident after intensive exercise bouts. CRP increased both after intense and moderate exercise, with peak increases up to 28h. CK increased only after intensive and long exercitation.

Conclusion: It is suggested a particularly caution due to increased susceptibility to illness when higher exercise intensities are used.

Keywords

Inflammation; exercise; high intensity; moderate intensity.

Resumo alargado

O exercício físico induz uma reposta inflamatória caracterizada pela mobilização de leucócitos, um aumento dos marcadores inflamatórios circulantes produzidos pelas células imunes e uma resposta direta no tecido muscular exercitado. Esta resposta depende das características, intensidade, duração, adaptação ao exercício, idade e condição clínica do atleta. Os marcadores inflamatórios compreendem a alteração do número de células no sangue periférico, atividade dos granulócitos, a função citotóxica das células Natural Killer (NK), a proliferação de linfócitos e os níveis plasmáticos de citocinas. Foram constatados tanto efeitos positivos como negativos sobre a função imunológica, assim como uma suscetibilidade para algumas doenças. Apesar da atividade física moderada ser reconhecida por melhorar a função imunológica comparativamente aos níveis observados em indivíduos sedentários, o exercício intenso prolongado pode induzir prejuízo sobre o sistema imunitário. O objetivo desta revisão sistemática foi clarificar a resposta inflamatória ao exercício moderado e intenso, em indivíduos saudáveis.

A pesquisa dos artigos para inclusão no estudo foi realizada na base de dados MEDLINE (PubMed) usando como expressão de pesquisa ("Inflammation"[Mesh]) AND ("Exercise"[Mesh]). Os critérios de inclusão consistiram em: estudos observacionais ou de intervenção, envolvendo adultos saudáveis (18-65 anos); escritos em inglês, português ou espanhol; incluindo exercícios moderados e/ou intensos. Esta seleção foi realizada tendo em conta os critérios PICO (*Population*, *Intervention*, *Comparison* e *Outcome*). Na definição da intensidade moderada e intensa do exercício foram usados vários parâmetros: escala de Borg, frequência cardíaca máxima (FC_{max}), frequência cardíaca máxima de reserva (FCR_{max}), consumo máximo de oxigénio (VO_{2max}), equivalentes metabólicos (MET), repetição máxima (RM) e MET por idade. As escalas STROBE e CONSORT foram utilizadas para verificar a qualidade dos artigos incluídos na revisão sistemática. As variáveis analisadas foram os números de leucócitos, linfócitos, células NK e sua atividade citolítica, bem como as concentrações séricas de IL-6, IL-8, IL-1ß, TNF-α, IL-10, proteína C reativa (PCR) e creatina cinase (CK).

Tendo em conta as recomendações estabelecidas pelas diretrizes de declaração *Preferred Reporting for Systematic Reviews and Meta-Analysis* (PRISMA) foram incluídos 18 estudos. Destes estudos foram retirados dados de 255 indivíduos saudáveis que praticaram diferentes modalidades (corrida, ciclismo, treino de força) em intensidades moderadas e/ou intensas. Os marcadores inflamatórios foram analisados a partir de amostras de sangue antes e após as sessões de atividade física, e as variações dos seus níveis foram apresentadas em número de vezes. A maioria dessas amostras foram recolhidas imediatamente após o exercício (10-15 min depois), tendo algumas delas sido recolhidas 30 min, 3 horas ou 72 horas após o exercício.

As citocinas IL-6, IL-8 e IL-10 mostraram aumentos imediatamente após o exercício, não tendo a IL-1ß e a TNF-α revelado alguma alteração. A IL-6 e IL-8 tiveram maiores aumentos no

exercício intenso, comparativamente ao exercício moderado. A IL-10 apenas mostrou aumento após o exercício intenso, sem alterações após o exercício moderado. No entanto, o impacto da duração do exercício deve ser considerado quando se comparam os resultados dos estudos. Relativamente aos leucócitos, após comparação das intensidades de exercício, verificou-se um aumento dos leucócitos apenas após o exercício intenso. No entanto, nas subpopulações de leucócitos (linfócitos) ambas as intensidades mostraram, na sua maioria, aumentos semelhantes. As células NK e a sua atividade citolítica foram apenas avaliadas por um estudo. Este mostrou um maior aumento após o exercício intenso do que após o moderado. Os marcadores inflamatórios CK e PCR mostraram maiores aumentos após o exercício moderado e intenso, respetivamente.

A maioria dos artigos em estudo mostraram alterações nos marcadores inflamatórios avaliados, mas essas alterações não se mostraram consistentes. Apesar disso, os resultados sugerem uma elevação dos mediadores pro-inflamatórios, especialmente pelo aumento da IL-6, seguidos do aumento da IL-10 (anti-inflamatória), mais evidente após exercício intenso.

Em conclusão, o exercício tem efeitos consideráveis sobre os marcadores inflamatórios. No entanto, os resultados desta revisão sistemática não foram consistentes, com discrepância provavelmente devido à enfâse da contração muscular e das características da modalidade praticada. Seria importante avaliar futuramente, não apenas a intensidade, mas as características do exercício e duração, uma vez que esses aspetos influenciam grandemente a inflamação dentro do grupo do exercício intenso. De um modo global, sugere-se um especial cuidado na realização de maiores intensidades, devido ao aumento da suscetibilidade a doenças.

Palavras-chave

Inflamação; exercício; alta intensidade; moderada intensidade.

O trabalho resultante desta dissertação de mestrado foi submetido na forma de artigo científico original ao Sports Health no dia 8 de Janeiro de 2019. O abstract da referente dissertação será apresentado em forma de poster numa Sessão temática no EEACI Congress 2019, em Lisboa, no dia 2 de Junho de 2019. (Annex 5 – Scientific Divulgation)

Index

List of Figures

List of tables

List of acronyms

CK - Creatine kinase

CONSORT - Consolidated Standards of Reporting Trials

CRP – C- reactive protein

HR_{max} - Maximal heart rate

HRR_{max} - Maximal heart rate reserve

IL – Interleukin

MEDLINE – MEDical Literatura Analysis and Retrieval System

MET - Metabolic equivalent

NK - Natural killer

PBMC - Peripheral Blood Mononuclear Cells

PICO - Population, Intervention, Comparison and Outcome

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analysis

RM - Repetition maximum

STROBE - Strengthening the reporting of observational studies in epidemiology

TNF-α - Tumor necrosis factor alpha

VO_{2max} – maximal oxygen consumption

WBC - White Blood Cells

1. Introduction

Inflammation is characterized by a cascade of cellular and molecular events leading to an increase in body temperature, capillary dilatation and production of pathological blood-borne soluble components. These responses, which can be induced by stressors and are vital for host defense and natural tissue homeostasis, initiate the elimination of noxious compounds and damaged tissue (1,2).

Exercise works as a stressor during and after its execution and is able to cause inflammation (3). Interestingly, however, regular physical exercise training may be considered a long-lasting anti-inflammatory therapy, after the acute inflammatory actions are resolved. Moreover, pro-inflammatory processes, such as increases in the expression of pro-inflammatory cytokines, which occur after acute exercise, may be vital for the long-term adaptive responses to exercise training. Consequently, exercise-induced changes in inflammation can be divided into acute effects (changes during and immediately following a bout of exercise) and longtime effects (changes in resting or basal levels, when the acute exercise-induced effects have been washed out).

Some authors have suggested that acute exercise bouts initiate a complex cascade of inflammatory events, which depend on the type, intensity, duration and familiarity of the exercise, as well as the age and clinical condition of the participants (1–6). Measurable immune parameters affected by exercise comprise changes in peripheral blood cell numbers, granulocyte activity, Natural killer (NK) cell cytotoxic activity, lymphocyte proliferation, and cytokine levels in plasma, among others (1,2,4–11).

Cytokines are soluble proteins or glycoproteins, produced and segregated during inflammation, that mediate the communication between immune and non-immune cells, and regulate biological processes (12). The production of cytokines can be up-regulated rapidly in response to inflammatory stimuli, and this response can be transient or prolonged. The pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) are released after physical activity of sufficient intensity, followed by the release of anti-inflammatory or regulatory cytokines (IL-4, IL-10, IL-1RA, IL-13) that attenuate that response (1).

Several proteins are affected in response to inflammatory processes, the majority showing increased levels shortly after an inflammatory reaction. Those proteins whose concentration increases are referred to as positive acute phase proteins. CRP is a hepatic acute phase protein, a marker of systemic inflammation and is associated with cardiovascular risk, without cause and effect relationship. Moreover, its levels have been correlated with frailty, morbidity and mortality. CRP has lower levels in people who do moderate exercise comparatively to inactive people (2,13). CK is a protein involved in muscle metabolism, and its concentration is generally considered a physical stress marker. Leakage of CK into the plasma is accepted as a semi-quantitative indicator of muscle fiber damage. CK levels have a significant variation with sex and race and also with

exercise type: eccentric exercise causing more muscle damage than concentric contractions of the same vigor (14,15).

Overall, it seems evident that there are immune changes after exercise, especially with increased intensity. Moreover, there is a belief that these changes differ markedly after heavy exercitation from those following moderate exercise. Therefore, this systematic review aimed to synthesize and analyze the moderate and intense physical activity in healthy active adults, to explore the associated inflammation markers, and to provide quantitative estimates on the change of these markers.

2. Methods

2.1. Search strategy

A comprehensive search in the MEDLINE (PubMed) database was conducted (16). The main target was to find studies that described immunologic changes in response to moderate and/or intense/vigorous exercise. The search expression ("Inflammation"[Mesh]) AND ("Exercise"[Mesh]) was used in all fields (Table 1). No limitation was made in publication date or duration of the study. Literature published from inception of the database up to 31 July 2017 was included.

Table 1. Search strategy and inclusion/exclusion criteria based on PICO.

Databases	Search terms	PICO	Inclusion criteria	Exclusion criteria
PubMed	Inflammation Exercise	Population	Healthy adults (18-65 years)	Sedentary adults; adults with disease
		Intervention	Moderate exercise	No exercise intensity definition
			Intense exercise	
		Comparison	Intense with moderate exercise	
		Outcome	Alterations in PBMC (WBC, lymphocytes, NK cells or NK cytolytic activity), Cytokines (IL-6, IL-8, IL-1ß, TNF-α, or IL-10), CRP, or CK	No results on inflammatory markers

CK: Creatine kinase; CRP: C- reactive protein; IL: Interleukin; NK: Natural killer; PBMC: Peripheral blood mononuclear cells; PICO - Population, Intervention, Comparison and Outcome; TNF-α: Tumor necrosis factor alpha; WBC: white blood cells.

2.2. Eligibility criteria

After the initial search, duplicates and studies not relevant for this analysis were excluded, and two independent reviewers examined the remaining studies' abstracts. Doubts regarding the inclusion or exclusion of studies were resolved by discussion between the two independent researchers. After this first selection, both researchers read though the articles to decide whether they were eligible using criteria defined with the PICO (Population, Intervention, Comparison and Outcome) criteria (Table 1) (17). The studies were eligible if they met the predefined inclusion criteria: a) observational (cross-sectional) OR interventional (randomized and non-randomized clinical trials) studies, b) conducted in healthy adults (18-65 years), c) written in Portuguese, English or Spanish, d) including moderate and/or intense exercise. Studies performed in sedentary adults, without exercise intensity definition, without results on inflammatory markers and systematic reviews were excluded. Further studies were considered for inclusion after verifying the references of the original studies.

Moderate exercise was defined by: Borg scale between 12-13 or % of maximal heart rate (HR_{max}) between 64 - 76 % or % maximal heart rate reserve (HRR_{max}) between 40 - 60% or % maximal oxygen consumption (VO_{2max}) between 46 - 64% or metabolic equivalent (MET) between 3 - 6 or % repetition maximum (RM) between 50 - 70 % or MET by age between 4.8 – 7.2 (young: 20 – 39 yr) and 4.0 - 6.0 (middle age: 40 – 64 yr). Intense exercise was defined by: Borg scale > 13 or HR_{max} > 76 % or HRR_{max} >60 % or VO_{2max} > 64 % or MET > 6.0 or RM > 70 % or MET by age > 7.2 (young: 20 – 39 yr) and > 6.0 (middle age: 40 – 64 yr) (18).

Scientific quality of the studies was assessed independently by two reviewers using the STROBE scale for cross-sectional studies and the CONSORT scale for clinical trials (Supplementary Material - table S1 and S2) (19,20). Studies complying with ≥ 75 % of the statements were considered to have good quality, 75 % - 50 % intermediate quality and ≤ 50 % bad quality. If assessment outcomes were conflicting, a consensus-based final score was attributed.

2.3. Data extraction

The main participants' characteristics and the main study outcomes were identified. Data regarding type, intensity and duration of the physical exercise and exercise-induced changes in inflammation markers were identified and appraised. The variables analyzed in this systematic review were PBMC (WBC, lymphocytes, NK cells and NK cytolytic activity), Cytokines (IL-6, IL-8, IL-1β, TNF-α, and IL-10), CRP, and CK.

This systematic literature review about inflammatory effects following high and moderate intensity exercise was registered in PROSPERO CRD42018085835 (21) and was performed according to the recommendations established by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement guidelines (22).

3. Results

3.1. Characteristics of the interventional studies

A total of 1374 records were identified through database searching and 7 additional records were identified through other sources, namely references in selected studies. After removal of duplicates, 1380 articles were considered for abstract reading. Following this first phase, 1339 articles were excluded. Of the 41 selected articles, only 39 were available as full-text and assessed for eligibility. After full-text reading 21 articles were excluded: 6 did not define the intensity and type of exercise, 4 included volunteers with disease, 4 were reviews, 1 was a letter, 1 was a comment, 4 were editorials and 1 did not refer to the inflammatory markers previously selected. After the application of these criteria, 18 studies were included for quality synthesis (Figure 1). Most of the included studies showed intermediate to good quality (Supplementary Material – Tables S1 and S2).

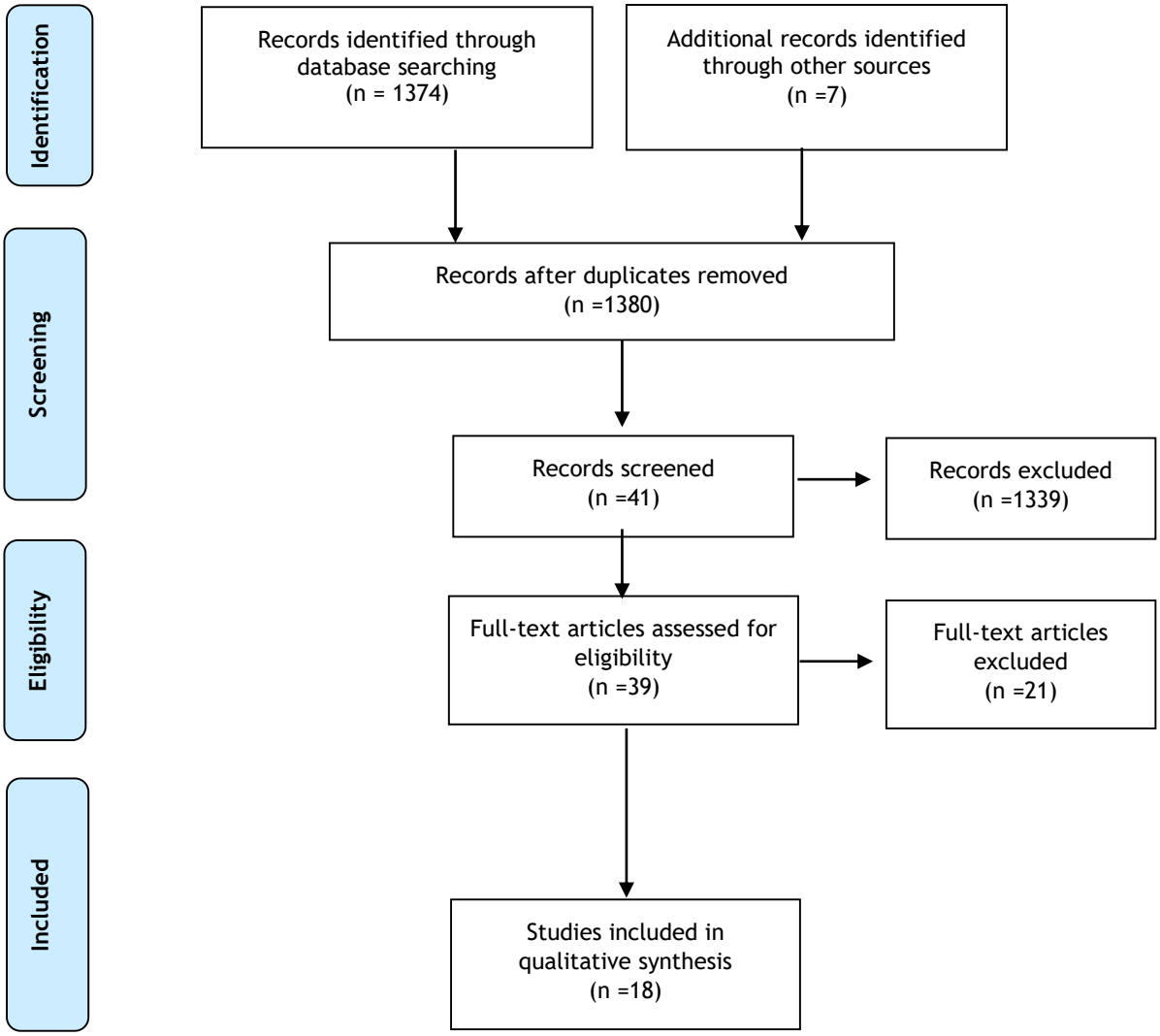

Figure 1 - PRISMA flowchart describing article selection.

The eighteen (18) included studies collected data from 255 healthy subjects. These participants performed different kinds of exercise interventions (running, cycling, resistance training and kayaking) in high and/or moderate exercise intensities. The age of the individuals ranged from 18 to 53 years (35.9 ± 17.0). Some of the results were from studies of mixed gender (23,24) and the remainder from male volunteers only (25,26,35–40,27–34). In the studies where the volunteers did more than one bout of exercise in different intensities, the resting period was highly variable: 1 month (25), 3 weeks (35), 2 weeks (30), 1 week (26,29,33) and 5 days (32). The characteristics of the included studies are summarized in Table 2.

The comparison in terms of inflammatory biomarkers between moderate and intense exercise is presented in Table 3. Inflammatory markers were evaluated in blood samples collected before and after the exercise bouts and relative increases related to base levels are shown (number of times). For most studies, blood samples were taken minutes after exercise (immediately, 10 or 15 minutes). However, some markers were evaluated at other time points: IL- 10 (26), WBC and lymphocytes (24) were evaluated also 30 minutes after exercise; WBC, IL-6, and TNF-α (39) were evaluated also 1 hour after exercise; IL-10 and TNF-α (30) were evaluated also 3 hours after exercise and CK (30) was evaluated also 3 days after exercise; CRP and CK (32) were evaluated also 4 days after exercise. Table 3 considers measurements collected up to 15 min after exercise. The results of IL-6 and CRP from Spiropoulos et al. (38) were not considered because they showed increases of 10470 and 6000 times, respectively, which makes them non-comparable with the other studies. The same occurs with the study from Marklund et al. (36) in which the baseline value of CRP was not detectable.

Table 2. Studies characteristics

Reference	Study type	Intensity and Description of exercise	Subjects	Inflammatory markers	Measure points	Findings
Gonzalo-Calvo et al. (25)	Cross-sectional	Intense: 10 km-race (89.12 % VO_{2max})	9 M Amateur runners Training experience: 6.6 ± 5.0 yr and 69.7±5.0 km/wk	PBMC: WBC, lymphocytes Cytokines: IL-6, IL-8 and IL-10 CRP CK	1.5 hours before exer, 10min, 1 day and 3 days after	↑ WBC, Lymphocytes and NK cells 10 min after exer ↑ CK from 10 min to 1 day after exer ↔ IL-8, IL-6, IL-10 and CRP
		Intense: HM (81.50 % VO_{2max})				↑ WBC, NK cells, IL-6, IL-10 and CRP 10 min after exer ↑ NK cells 10 min and 1 day after exer ↑ CK and CRP from 10 min to 1 day and ↓ after that ↔ Lymphocytes and IL-8
		Intense: Marathon (68.70 % VO_{2max})				↑ WBC, NK cells, IL-6, IL-8, IL-10 and CRP 10 min after exer ↑ CK and CRP from 10 min to 1 day and ↓ after that ↔ Lymphocytes

Wadley et al. (26)	Cross-sectional	Intense: LV-HIIE (90% VO_{2max}) and high (80% VO_{2max}) 10 x 1min cycling of LV-HIIE with 1 min interval 20 min cycling of high exercise	10 M Untrained	PBMC: Lymphocytes Cytokines: IL-6 and IL-10	Before, at the end and 30 min after exer	↑ Lymphocytes at the end, returns to baseline in 30 min ↑ IL-10 30 min at the end ↑ IL-6 at the end and 30 min after exer
		Moderate: cycled for 27 min (60% VO_{2max})				↑ Lymphocytes at the end and returns to baseline in 30 min ↑ IL-6 at the end and 30 min after exer ↔ IL-10
Ulven et al. (33)	Cross-sectional	Intense: Cycled for 1 hour repeated twice (70 % VO_{2max}, % HR_{max} ≅ 87.8% and Borg scale ≅ 15.4)	10 M Very good physical fitness	Cytokines: IL-6, IL-10 and TNF-α	Before and at the end of cycle test	↑ IL-6, IL-10 and TNF-α at the end of exer
Azizbeigi et al. (34)	Controlled Trial	Intense: Resistance training (85-90 % of 1RM) 3 sets of 10-12 repetitions and 1-2 min rest between sets	30 M (10 control, 10 moderate intensity and 10 high intensity) Untrained but physically active (running, volleyball or soccer)	Cytokines: IL-6 and TNF-α CK	Before, at the end and 3 days after training program	↔ IL-6, TNF-α and CK

		Moderate: Resistance training (65-70 % of 1RM) 3 sets of 3-6 repetitions and 3-4 min rest between sets				
Stelzer et al. (23)	Cross-sectional	Intense: Cycling race (98.68 % HR_{max}) 8 hours of competition and 8h of rest during 4 days	7 (3 F : 4 M) Moderately trained amateur athletes Training experience 7.5 ± 3.9 h/wk;	PBMC: WBC and lymphocytes Cytokines: IL-6 CK	2 days pre-race and 15 min post-race	↑ WBC, lymphocytes, IL-6 and CK post-race
Abbasi et al. (24)	Cross-sectional	Intense: HM in competition conditions (V ≅ 13.26 km/h for men and 11.11 km/h for women) Timing: 95.5 ± 8 min for men and 114 ± 12 min for women	16 (8 F : 8 M) Well trained athletes Training experience: endurance training for at least 2 yr;	PBMC: WBC and lymphocytes;	Before, 30 min, 3 h and 24 hours after exer;	↑ WBC at 30 min and 3h after exer ↓ Lymphocytes at 30 min and 3 h after exer
Draganidis et al. (35)	Cross-sectional	Intense: Resistance training: squat, seated leg extension, horizontal leg curls, barbell side lunges, and calf raises; (85-90 % 1 RM)	10 M Elite football players Training experience: 6 training sessions/wk	PBMC: WBC CRP CK	After, at the end, and daily for 3 days after the exer	↑ CRP at the end to 1 day and after returns to baseline ↑CK at 2 days and after returns to baseline ↔ WBC

		4 sets, 4-6 repetitions per set with 3 min rest Training during around 40-45 min following of 10 min warm-up				
		Moderate: Resistance training: squat, seated leg extension, horizontal leg curls, barbell side lunges, and calf raises (65-70 % 1 RM) 4 sets, 8-10 repetitions per set with 1 min rest Training during around 40-45 min following of 10 min warm-up				↑ WBC and CRP at 1 day and after returns to baseline Higher elevation in CRP, at the end and 24 h after exer ↑ CK at 1 day and after returns to baseline
Marklund et al. (36)	Cross-sectional	Moderate: 24 hours ultra-endurance exer: running, cycling and kayaking (46 – 63 % VO_{2max}); 12 sets of 110 min of exer with 10 min rest for food intake	9 M Well trained ultra-endurance athletes Training experience: competed in races with long distance (>48h)	PBMC: WBC Cytokines: IL-6, IL-8, IL-1ß and TNF-α CRP CK	Before, at the end and 28 h after the exer	↑ WBC, IL-6 and CK at the end and ↓ 28 h after exerc ↑ IL-8 and CRP at the end and further ↑ at 28 h ↔ TNF-α and IL-1ß

Nieman et al. (37)	Cross-sectional	Intense: 1.75 hours cycling followed by 10 km time trial as fast as possible (18.3 ± 1.7 min) total of 2.1 hours cycling (Borg scale = 13.3 ± 1.1 and 82.2 % ± 6.1 % HR max)	31 M Trained cyclists Training experience: cycling 75 km	PBMC: WBC and lymphocytes Cytokines: TNF-a, IL-6, IL-8, IL-10 and IL-1ß	before, at the end and 1 h post exer	↑ WBC and lymphocyte at the end and ↓ 1 h after exer ↑ TNF- α, IL-6, IL-8, IL-10 and IL-1ß at the end of exer ↓ TNF-α, IL-6 and IL-8 1 hour after; IL-10 and IL-1ß continued to ↑ 1 hour after
Bernecker et al. (39)	Cross-sectional	Intense: Marathon (89.3 % HR_{max})	12 M Training experience: Finished HM before	PBMC: WBC Cytokines: IL-6 and TNF- α	Before and 1 h after exer	↑ WBC, IL-6 and TNF-α 1 hour after exer
Spiropoulos et al. (38)	Cross-sectional	Intense: Ultra-endurance foot race over a distance of 246 km (9.08 MET by middle age) Finished the race in <36 hours	10 M Training experience: done an equal race before	PBMC: WBC Cytokines: IL-6; CRP	Before, at the end and 2 days after race	↑ WBC, IL-6 and CRP at the end of exer, IL-6 and WBC return to baseline 2 days after but CRP still ↑
Fatouros et al. (32) *	Cross-sectional	Intense: 4 x 3 wk resistance training period divided in t1, t2, t3 and t4 t1 and t4: low-volume 70 % 1 RM (t1 and t4), 75 % – 85 % 1 RM (t2) and 85 % – 100 % 1 RM (t3);	17 M Amateur athletes	CRP CK	Before and 96 h after each session of exer	↑ CRP after t2 and t3 ↑ CK after t3 and t4

		2 times per wk, 2 sets per exer, 10-12 repeats per set t2: high-volume training (4 times per wk, 4 sets per exer, 6-10 repeats per set) t3: very-high-volume training (6 times per wk, 6 sets per exer, 1-6 repeats per set);				
Degerstrom et al. (40)	Cross-sectional	Intense: 2 sets of 30 min run with 4 hours rest (80 % VO_{2max})	7 M 5 elite skiers and 3 competing at the district level Training experience: 1 to 2 times/day	PBMC: WBC and lymphocytes Cytokines: IL-6 and IL-8	Before, at the end each run and 2 h after second run	WBC: ↑ at the end 1st race; ↓ before 2nd race; ↑ more at the end 2nd race than 1st; ↓ 2 h after 2nd race; Lymphocytes and IL-8 ↑ after 1st and 2nd run, and IL-8 ↓ 2 h after 2nd race ↔ IL-6
Connolly et al. (27)	Controlled Trial	Intense: 30 min cycling (80 % VO_{2max})	15 M Amateur athletes	PBMC: WBC and lymphocytes Cytokines: IL-6	Before, at the end and 1 h after exer	↑ WBC and lymphocytes at the end of exer and return to baseline ↑ IL-6 1 h after exer
Bonsignore et al. (28)	Cross-sectional	Intense: Marathon (15.07 MET by middle age)	8 M Amateur athletes Training experience: 77 ± 15 km/wk and 14 ± 10 yr	PBMC: WBC and lymphocytes	After and at the end of exer	↑ WBC at the end of exer ↓ Lymphocytes at the end of exer

Mucci et al. (29)	**Controlled Trial**	Intense: (75 % and 100 % of VO_{2max}); Moderate: (50 % of VO_{2max}); Cycling at 30 Watts for untrained and 60 watts for trained athletes with successive increases of 30 watts every minute (at the end of test the increase was smaller)	22 M 11 highly trained endurance athletes (athletes group) Training experience: 5.2 ± 06 yr and 16.3 ± 1 hour/wk	Cytokines: IL-1ß and IL-8	Before the exer, at 50 % VO_{2max}, 75 % VO_{2max}, 100 % VO_{2max} and recovery (5 min after)	↑ IL-1ß both intensities and returns to baseline in recovery ↑ IL-8 both intensities and returns to baseline in recovery
			11 untrained group but physically active (control)			↑ IL-8 at 100% VO_{2max} ↔ IL-1ß
Brenner et al. (30) #	**Randomize controlled Trial**	Intense: Cycling for 5 min (90 % VO_{2max})	8 M Moderately fit	PBMC: NK cells and NK Cytolytic activity Cytokines: IL-6, TNF-α and IL-10 CK	30 min before, at the end, 3 h, 1 day and 3 days after each test	↑ NK cells at the end of exer and return to baseline 3 h after ↑ Citolytic activity at the end of exer; ↓ IL-10 from 3 h to 3 days after ↔ IL-6, TNF- α and CK
		Upper limit of moderate: 2 hours cycling (60 % - 65% VO_{2max})				↑ NK cells at the end of exer and return to baseline 3 h after ↑ Citolytic activity at the end of exer ↑ IL-6 at the end to 3 h after exer ↑ TNF-α from 3 h to 3 days after exer ↔ IL-10

		Moderate: 3 sets of 10 repeats in resistance training (bicep curl, knee extension, hamstring, curl, bench press and leg press) (60 % - 70 % 1 RM)				↑ NK cells at the end of exer and return to baseline 3 h after ↑ CK 3 days after exer ↔ IL-10, IL-6, IL-10 and NK cells cytolytic activity
Ostrowski et al. (31)	Cross-sectional	Intense: Marathon (75.33 % $VO2_{max}$)	10 M	Cytokines: TNF-α, IL-1β, IL-6 and IL-10	1 wk before, at the end and every 30 min in the 4 h after exer	↑ TNF-α, IL-1β, IL-6 and IL-10 at the end ↓ IL-10 and IL-6 (immediately) ↓ TNF-α and IL-1β (slowly)

↑: significant increase; ↓: significant decrease; ↔: no change; 1 RM: one repeat maximum; 1st: first; 2nd: second; CK: creatinine kinase; CRP: C-reactive protein; Exer: exercise; F: Female; h: hour; HIGH: high intensity; HM: half marathon; HR_{max}: maximum heart rate; IL: Interleukin; LV-HIIE: High intensity interval exercise; M: male; PBMC: peripheral blood mononuclear cel; TNF-α: Tumor necrosis factor alpha; V: velocity; VO_{2max}: maximum rate of oxygen consumption; WBC: white blood cells; wk: week; yr: years; * <75% in STROBE quality scale; # <75% in CONSORT quality scale;

Table 3. Immediate effects of moderate and intense exercise (0-15 min) on inflammatory markers

Inflammatory marker	Moderate exercise	Reference	Intense exercise	Reference
WBC	↔	Draganidis et al. (35) Marklund et al. (36)	↑] 1.44; 3.5 [x	Gonzalo-Calvo et al. (25) Stelzer et al. (23) Nieman et al. (37) Spiropoulos et al. (38) Degerstrom et al. (40) Connolly et al. (27) Bonsignore et al. (28)
			↔	Draganidis et al. (35) Abbasi et al. (24) Bernecker et al. (39)
Lymphocytes	↑ 1.41 x	Wadley et al.(26)	↑] 0.83; 2.69 [x	Gonzalo-Calvo et al. (25) Wadley et al.(26) Stelzer et al. (23) Nieman et al. (37) Degerstrom et al. (40) Connolly et al. (27)
			↓] 1.56; 4.21 [x	Bonsignore et al. (28)
			↔	Abbasi et al. (24)
NK cells	↑ 5.5 x	Brenner et al. (30)	↑ 8.83 x	Brenner et al. (30)
NK cells cytolytic activity	↑ 2.92 x	Brenner et al. (30)	↑ 4.63 x	Brenner et al. (30)
IL-6	↑] 1.33; 4.20[x	Wadley et al.(26) Brenner et al. (30)	↑] 1.59; 26.79 [x	Gonzalo-Calvo et al. (25) Wadley et al.(26) Ulven et al. (33)

				Stelzer et al. (23) Nieman et al. (37) Spiropoulos et al. (38) * Connolly et al. (27) Otrowski et al. (31)
	↔	Azizbeigi et al. (34) Marklund et al. (36)	↔	Azizbeigi et al. (34) Degerstrom et al. (40) Brenner et al. (30) Bernecker et al. (39)
IL-10	↔	Wadley et al. (26) Brenner et al. (30)	↑] 1.57 ; 32.99 [x	Gonzalo-Calvo et al. (25) Ulven et al. (33) Nieman et al. (37) Ostrowski et al. (31)
			↔	Brenner et al. (30) Wadley et al. (26)
IL-8	↑ 1.43 x	Mucci et al. (29)	↑] 1.37; 2.77 [x	Gonzalo-Calvo et al. (25) Nieman et al. (37) Degerstrom et al. (40) Mucci et al. (29)
	↔	Marklund et al. (36)		
IL-1β	↑ 1.13 x	Mucci et al. (29)	↑] 1.13; 1.50 [x	Nieman et al. (37) Mucci et al. (29) Ostrowski et al. (31)
	↔	Marklund et al. (36)		
TNF-α	↔	Azizbeigi et al. (34) Marklund et al. (36) Brenner et al. (30)	↔	Azizbeigi et al. (34) Brenner et al. (30) Bernecker, 2011
			↑] 1,30; 2.07 [x	Ulven et al. (33)

				Nieman et al. (37)
				Ostrowski et al. (31)
CRP	↑ 1.23 x	Draganidis et al. (35)	↑ 1.4 x	Draganidis et al. (35)
		Marklund et al. (36)#		Spiropoulos et al. (38)*
			↔	Gonzalo-Calvo et al. (25)
				Fatouros et al. (32)
CK	↑] 1.92; 24.16 [x	Draganidis et al. (35)	↑] 2.19 ; 4.75 [x	Gonzalo-Calvo et al. (25)
		Marklund et al. (36)		Stelzer et al. (23)
				Draganidis et al. (35)
	↔	Azizbeigi et al. (34)	↔	Azizbeigi et al. (34)
		Brenner et al. (30)		Brenner et al. (30)
				Fatouros et al. (32)

↑: significant increase; ↓: significant decrease; ↔: no change; CRP: C-reactive protein; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; WBC: white blood cells; * Spiropoulos et al. wasn't included to calculate the increase interval of IL-6 and CRP due very discrepant values after exercise when compared to the other studies (10470 and 6000 times, respectively); # Marklund et al. wasn't included to calculate the increase interval of CRP due baseline value was not detectable.

3.2. Effects of exercise on cytokine secretion

Fifteen studies evaluated the effects of exercise on cytokine concentration in blood (IL-6, IL-8, IL-1β, IL-10, and TNF-α). Our review supports, in general, the idea that exercise can stimulate both pro- and anti-inflammatory responses. These increases were transitory, with the values returning to baseline sometime from 5 to 24 hours after exercise.

IL-6 was the cytokine more often evaluated (13 studies) corresponding to 4 moderate and 12 intense exercise bouts. There were increases in IL-6 after exercise ranging from 1.33 to 4.20 times in moderate and from 1.59 to 26.79 in high intensity exercises, immediately after exercise. In 6 studies there was no increase (2 moderate and 4 intense exercises) (30,34,39,40).

IL-8 was evaluated in 5 studies (25,29,36,37,40), with increased levels after moderate exercise of 1.43 times and after intense exercise ranging from 1.37 to 2.77 times.

IL-10 was evaluated in 6 studies, with increased levels after intense exercise ranging from 1.57 to 32.99 times in 4 studies (25,31,33,37). In 3 studies there was no increase, 1 of these referred to intense and moderate exercise, 1 to moderate and 1 to intense exercise only.

Gonzalo-Calvo et al. (25) evaluated the effect of different doses of aerobic exercise (moderate and intense) on circulating IL-8, IL-6 and IL-10, and observed an increase in all the evaluated cytokines. This rise was maintained for 1 day or more and then returned to baseline. Similar cytokine elevations were found in other studies (36,38). Wadley et al. (26) evaluated the cytokine profile after moderate and intense cycling exercise. Their results show an increase in IL-6 at 30 min after exercise independently of intensity, without information after that. In the same study IL-10 increases 15 min after intense exercise, without alteration in moderate exercise. Mucci et al. (29) evaluated cycling intense and moderate exercises showing a transient increase in IL-8 in both intensities with return to baseline values after 5 minutes. Brenner et al. (30) evaluated cytokine levels after moderate and intense exercise but only show an increase in IL-6 after moderate exercise, which peaked at 3h and returned to baseline values 28 hours after exercise (recovery).

Some studies that evaluated only intense exercise showed an increase in IL-6, IL-8, and IL-10; however, values peaked at different times: immediately (15 min) for IL-6 and IL-10 in Ostrowski et al (31), 1 or 2 hours after exercise for IL-6, IL-8 and IL-10 in Nieman et al. (37) and for IL-8 in Degestrom et al. (40). Marklund et al. (36) that evaluated moderate ultra-endurance exercise showed an increase in IL-8 and IL-6, 30 min after exercise, however only for IL-8 did this increase remained at 28 hours. Spiropoulos et al. (38) evaluated an intense ultra-endurance exercise and observed an increase of IL-6 maintained at 2 days but this increase is not shown in table 3 because it is very discrepant from other studies (increased 10470 times). The same was observed for the studies by Gonzalo-Calvo et al., Ostrowski et al. and Benecker et al. (25,31,39) This discrepancies might be explained by the duration of the exercises in those studies: the Spiropoulos study refers to ultra-endurance exercise, and the remainder three studies to marathon races (25,31,39).

Globally the increase in IL-6 and IL-8 levels was higher in intense when compared to moderate exercises. In contrast, IL-10 only showed increases after intense exercise, with no changes after moderate exercise (Supplementary Material - Figures S1 and S2) (25,26,30,31,33,37). Nevertheless, the impact of the duration of the exercise bout should be considered when comparing the studies' results.

IL-1β was evaluated in 4 studies (29,31,36,37) with discrepant results. Mucci et al. (29) reported approximately the same increase and return to baseline in both exercise intensities for IL-1β. The same pattern was reported in intense exercise by Nieman and Ostrowski (31,37). In contrast, Marklund and colleagues (36) reported no changes in this cytokine.

TNF-α was evaluated in 8 studies corresponding to 3 moderate exercise types without alteration (30,34,36) and 6 intense exercise types: 3 with no alteration on the cytokine levels (30,34,39) and 3 with increases immediately after exercise (31,33,37). All the studies with alteration had exercise times of more than 1 hour. Only the study by Ostrowski et al. (31) had repetitive measurements showing a slow decrease in TNF-α values without returning to base levels after 4 hours.

3.3. Effects of exercise on peripheral blood leukocytes

Eleven studies evaluated the effect of exercise on WBC: 1 for intense and moderate exercise without alterations in both (35), 1 for moderate exercise without alterations (36), 7 for intense exercise with increased numbers of WBC (23,25,27,28,37,38,40) and 2 for intense exercise without alterations (24,39).

Abbasi et al. (24) evaluated the effect of half-marathon running (high intensity exercise) and observed an increase in WBC numbers 30 min after exercise. This elevation was maintained even after a 3 hours recovery period and reflected a pronounced granulocytosis. In contrast, lymphocyte count had no alterations in the same period but increased 30 min after exercise. All leukocyte counts returned to normal 24 hours post-exercise (24). Similar to this study, Bonsignore et al. (28) showed an increase of WBC and a decrease of lymphocytes, but these alterations were transient returning to baseline immediately after exercise. This increase of WBC occurred due to neutrophils and macrophages.

Nieman et al. (37) that analysed the influence of prolonged cycling in high intensity in acute inflammatory response showed an increase in WBC, but, in contrast to previous studies, this occurred due to increased lymphocytes, monocytes and granulocytes. Lymphocytes and WBC returned to baseline 1 hour after exercise. The same pattern occurred in other 3 studies: Degerstrom et al. (40) with increases at 2 hours after exercise, Connolly et al. (27) with increased at 1 hour after exercise and Stelzer et al. (23) with increases immediately after exercise. These increases in WBC were reportedly due to lymphocytes and granulocytes in the Degerstrom et al. (40) study; due to neutrophils, monocytes and lymphocytes in the Stelzer et al. (23) study; and due to lymphocytes and monocytes in the Connoly et al. (27) study.

Other 2 studies of intense exercise also evaluate WBC showing increases after exercise, but do not have data on relevant subpopulations (38,39).

Draganidis et al. (35) analyzed WBC after resistance training (intense and moderate exercise) showing an increase after moderate exercise, which return to baseline 1 day after, and did not report alterations in WBC after intense exercise. Wadley et al. (26) evaluated lymphocytes but not total WBC after cycling exercise (moderate and intense) and reported an increase in both intensities that returns to baseline 30 min after exercise. Marklund et al. (36) evaluated WBC 30 min after moderate exercise showing an increase with return to baseline values 28 hours after exercise.

When comparing both exercise intensities, the increase in total leukocytes only occurs after intense exercise. However, in the lymphocytes subpopulation both intensities showed similar increases, with only 1 study presenting a decrease in lymphocytes after intense exercise (28).

One study specifically considered NK cell numbers and NK cytolytic activity: Brenner et al. (30) showed an increase in both parameters after exercise. This increase was greater in intense exercise when compared to moderate exercise.

3.4. Effect of exercise on creatine kinase

CK was evaluated in seven studies corresponding to 10 different exercise types. In short, CK increased in 3 intense type exercises (23,25,35) and 2 moderate exercises (35,36), with no alteration in the remainder studies evaluating moderate and intense exercise in the same volunteer group. In the study of Draganidis et al. (35) the increase in CK peaked at 24 hours after exercise in the moderate intensity group, while it peaked at 48 hours in the high intensity group. However, in the study by Gonzalo-Calvo et al. (25) CK peaked 24 hours after intense exercise and in the study by Marklund et al. (36) 28 hours after moderate exercise. Fatouros et al.(32) evaluated CRP 4 days after exercise showing an increase. Comparing intense and moderate exercise, the increase in CK was] 2.19; 4.75[and] 1.92; 24.16 [, respectively. This increase was greater in moderate exercise, but only 2 studies evaluate this intensity when compared to 4 studies evaluating intense exercise.

3.5. Effect of exercise on C reactive protein

CRP was evaluated in 5 studies (25,32,35,36,38), with 1 study evaluating both intensities (35). Increases in CRP were observed in 2 study of moderate exercise (35,36) and 2 studies of intense exercise (35,38). In the Draganidis et al. (35) study the elevation was maintained for 1 to 2 days before returning to baseline. Gonzalo-Calvo et al, (25) just had elevations of CRP at 24 hours after exercise, without alterations before that. Fatouros et al.(32) evaluated CRP 4 days after exercise showing an increase. Globally, all the studies had increases of this inflammatory marker, with greater values at 24 hours. Comparing both exercise intensities, the increase was bigger after intense exercise, but only one study referred to moderate intensity exercise.

4. Discussion

This systematic review evaluated the changes of inflammatory markers after moderate and intense exercise bouts. The findings of the current review suggested that there is an acute inflammation profile after exercise, with the increase of most inflammatory markers, especially in high-intensity exercise.

4.1. Exercise-Induced effects on cytokines

Results suggested that there are substantial discrepancies in the extent of pro-inflammatory changes in the immune system. By examining the impact of different intensity exercise on anti-inflammatory cytokines secretion, some of the studies showed an increase while others report no change. (30,34,36,39). This might be a consequence of cytokines appearing only transiently in the blood and thereby evading detection. Moreover, cytokines are secreted by many cells and tissues, with muscle considered to be a major contributor during exercise, as such, circulating levels might not reflect levels in source tissues.

IL-6 concentration increases more than other cytokines during exercise what might indicate muscle damage (2,10). IL-6 plasma concentrations are reportedly affected by factors other than intensity, such as type and time of exercise (11,15). It is a pleiotropic cytokine involved in exercise adaptation, in processes of angiogenesis and hypertrophy (41) and exerting also anti-inflammatory effects mediated by the inhibition of TNF-α and IL-1 production (7). IL-6 stimulates glucose availability during exercise and, with training, the muscle can become more efficient in fuel utilization during moderate to intense exercise. Persistent elevation of this cytokine can be associated with muscle atrophy, that results in reduction on strength and muscle function and increased muscle pain (6). Following acute exercise, elevated levels of IL-6 promote an increase in IL-10 and IL-1RA, two anti-inflammatory cytokines.

Most studies showed an increase in IL-10 after intense exercise which is consistent with previous reports (1,2). Shaw et al. (8) demonstrated that IL-10 production, after strenuous acute exercise, is equivocal, with increases, decreases and no changes in exercises with different protocols and analytical techniques. Regardless, levels of IL-10 tend to peak during recovery time from exercise, with the magnitude of the increase being related to the active muscle mass and exercise intensity. Overall, the duration of the exercise was the most important factor determining the magnitude of the exercise-induced increase of plasma IL-10, as recently reviewed by Cabral-Santos et al.(42) This increase in IL-10 could be related to the prevention of potential deleterious chronic low-grade inflammation and tissue damage.

TNF-α was only stimulated by intense endurance exercise (more than 1 hour) (31,33,37). In contrast to our main findings, Starkie et al. (43) showed that the production of TNF-α decreased after a single endurance exercise bout and Moldoveanu et al. (1) reported an increase in TNF-α after three 2-3 hours moderate bouts (cycling and run + cycling). However, Moldoveanu et al. (1)

found no change after a single 45 min moderate bout or one 5 min intense bout. These results suggest that other factors, namely exercise duration, are also important in regulating TNF- α release.

Previous reports suggested that IL-1 release depends on the type, intensity and duration of exercise (1). Our review shows that IL-1ß increases in all studies of intense exercise but in none after moderate exercise. Similar to TNF-α, the local increase of IL-1 is higher than the systemic increase, after eccentric exercise (15). IL-1ß is a potent pro-inflammatory cytokine, influencing adhesion molecules and chemokines, and by this, possibly relating to leukocyte migration and function.

IL-8 is produced by endothelial cells, monocytes, macrophages, fibroblasts, neutrophils and T lymphocytes and acts as a chemokine. Its expression is up-regulated by IL-1 and various other stimuli. In this systematic review it was observed that IL-8 increased after both exercise intensities, which is consistent with previous reviews that report increased IL-8 systemic levels associated with damaging exercise regimes (1,10). Suzuki et al. (44) showed that IL-8 increases after prolonged exercise, with some alteration after acute intense exercise. The same occurs in this systematic review, with IL-8 systemic levels increasing after prolonged and acute intense exercises.

In general, cytokines increase more with intense than with moderate exercise, but these increases are not consistent, being influenced by the duration and type of exercise.

4.2. Exercise-Induced effects on CK

CK results were very discrepant, as half of the articles showed no alterations immediately after intense or moderate exercise, while the other half showed an increase of CK levels. Moghadam-kia et al. (14) refered that CK levels have a significant variation with sex and race. The degree of this change depended on the duration and type of exercise; with strenuous exercise being responsible for greater elevations. Damaged muscle fiber structures were pointed as being the cause for the rise, but one study of repeated eccentric exercise caused almost no increase on CK levels (15). CK was the only marker whose increase was higher in moderate when compared to intense exercise, but few studies were available in the moderate exercise arm.

4.3. Exercise-Induced effects on CRP

The immediate response to inflammatory stimuli is termed the acute phase response and includes a set of proteins produced primarily in the liver in response to cytokines such as IL-6, TNF-α, and IL-1 (7,45–47). Of the proteins stimulated during the acute phase response, CRP has received the most attention as a marker of inflammation in both rheumatic and nonrheumatic diseases (7,48). CRP is a member of the pentraxin family; although its function is not fully known, it is proposed to have a scavenger function to eliminate bacterial products or damaged cells and to attenuate the consequences of infection or tissue injury (48). Petersen et al. (7) refer that this inflammatory marker has a role in the suppression of the synthesis of pro-inflammatory cytokines

by tissue macrophages and in the induction of anti-inflammatory cytokines. Because the levels of CRP increase dramatically during inflammation processes and remain elevated for a long period of time CRP can be a suitable marker. In intense exercise of this systematic review the studies (32,35) had an increase of CRP at the end of exercise in contrast of Petersen et al, (7) when CRP increase one day after. This discrepancy can occur once in this articles the athletes did short sets of exercise and in Petersen et al. (7) they practice longer duration exercise Fedewa et al. (13) indicates that CRP had a significant and small decrease following training, but doesn't report values immediately after acute exercise. This information is in opposition to Petersen et al. (7) reports, showing that regular exercise induces reduction in CRP. In general, the muscle damage, as evidenced by CK activity was not accompanied by parallel increases in inflammatory markers, namely cytokines and CRP.

4.4. Exercise-Induced effects on WBC

An acute bout of exercise induces the mobilization on WBC into the peripheral blood compartment. Peake et al. (4) showed that a single bout can cause changes in blood number of leukocytes, which persist during exercise recovery and in contrast, decrease faster (in 30 min) after especially prolonged and/or intense exercise. The included studies showed a WBC increase immediately after intense exercise; however, in the recovery period the decrease was inconsistent between studies. WBC number was the only inflammatory marker studied that showed a clear increase after intense exercise in all the included studies, without alteration in moderate exercise studies. The results also suggest a chronology in the mobilization of the different leukocyte populations to the blood, with lymphocytosis occurring at the end of the intense exercise bouts and decreasing shortly after (30 min) (26).

NK cells are innate cytotoxic effectors of the immune system, which under physiological conditions can distinguish between healthy autologous cells and target cells. As a part of the innate immune system, NK cells can recognize and eliminate neoplastic and virus infected cells without prior contact (5). Decrease in NK activity is accompanied by an increase incidence of infectious diseases (49). NK cell number and NK cell activity increased after moderate and intense exercise, but this was just verified in one study included in this systematic review. The study by Brenner et al. (30) showed that acute physical exercise increased the activity and induced mobilization of NK cells to the peripheral blood independently of exercise intensity. Theoretically, a high frequency of NK cells can possibly protect the body against infections or tumor progression, but it must be bared in mind that these increases were transitory, and possible migration of NK cells to peripheral tissues was not assessed. Previous reviews reported NK and NK activity increases in response to stressors (4,5,9,50).

Studies that explore the true effect of changes in cell distribution in response to exercise and health status are lacking, and the relevance of these findings cannot be fully appraised as we failed to consider the number of cells infiltrating in the muscle tissue in response to exercise. In

fact, Marklund et al. (36) show that a moderate-intensity endurance activity (60% $_{V02max}$) sustained during a very prolonged period induced an extensive local muscle infiltration.

4.5. Implications for practice

Exercise has been established as a part of multimodal therapeutic approaches in several pathologies contributing to cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance. However, the strong variability in study designs; type, duration and intensity of exercise remain obstacles in the assessment of the measurable effects of exercise on inflammatory markers.

A recent systematic review on the impact of physical activity on serum levels of inflammatory markers in rheumatoid arthritis patients failed to conclude that there is a significant impact on systemic levels of inflammatory markers.(51) Effects of medication on inflammatory markers, concerns about potentially increasing pain and exacerbation and disease activity have also to be considered in this setting.

Previous studies suggested that the effect of aerobic exercise on the cytokines' increase is different from the effect of strength/ resistance exercise, with the latter being less evident.(42) This is in line with our evidence. Moreover, strength/resistance exercises are influenced by different variables such as intensity, workload, number of repetitions, the interval between sets, and size of muscle mass involved in muscle contraction. Whereas the anti-inflammatory nature of IL-6 contributes to the acute phase response and the adaptation of skeletal muscle to exercise, chronically elevated levels of IL-6 contribute to persistent inflammation and muscle wasting.(10) The release of anti-inflammatory mediators, such as IL-10, as a compensatory mechanism, might also impair immune responses. The pronounced anti-inflammatory response induced by prolonged and exhaustive exercise could lead to transient suppression of several immune components and increase the risk of infection.(8)

4.6. Limitations

The results of this review were based on individual sports, such as cycling, resistance training, running and kayaking, which limits its application to other types of sports. Some limitations were found in the compilation and comparison of results because the time, type of exercise, and number of bouts were different among studies. In addition, we did not perform a comparative analysis (meta-analysis), because such analysis could not be easily accomplished due to the lack of consistency in parameters and the lack of uniformity. Because of the non-response of some study's authors, some articles with important findings might not be included. CRP was the most restrictive inflammatory marker, with no possible comparison of concentrations since measurement methods varied widely. Our findings showed that most studies follow the same pattern of changes; however, the amplitude of those changes at the systemic level does not always correlate with exercise-induced changes in local inflammation. Another limitation is that most of studies performed the

experiment at a single level of intensity with a relative small number of participants, which might have contributed to increase the individual variability. All the studies included in this systematic review refer to healthy non-sedentary individuals. As such, it is not possible to ascertain if the same results would be valid for sedentary individuals that initiate exercise practice and what would the implications be in populations with chronic inflammatory pathologies.

5. Conclusion

Based on the current review findings, exercise has considerable effects on inflammation markers. Pro-inflammatory cytokine TNF- α and anti-inflammatory IL-10 only increases after intense exercise, and pro-inflammatory cytokines IL-6 and IL- 1β increase more with intense than with moderate exercise. The main differences regarding the effect of intensity of exercise on the inflammation markers studies were found in total WBC, IL-6 and IL-10, with higher increases in intense than in moderate exercise bouts. The highest alterations occur after intense exercise in IL-6 with increases up to 26.79 times and in IL-10 with increases up to 32.99 times, corresponding a $VO2_{max}$ of 75.33 % (31). In moderate exercise studies, higher alterations occur in CK with an increase 24.16 times at a $VO2_{max}$ of 46 – 63 % (36). However, our results were not consistent, with discrepancies probably due to the emphasis on muscle contraction (eccentric versus concentric) and intensity of the effort related to the kind of the exercise. Nevertheless, and although regular exercise presents a global positive anti-inflammatory effect, high-intensity exercise, especially when performed with reduced recovery periods, induces a persistent dysregulation of the immune system with increased susceptibility to illness. Further research is required to examine the impact of exercise intensity on inflammation. It is important that future studies carefully assess not only intensity, but associate it with exercise type and duration, as those aspects were found to deeply influence inflammation within the intense exercise group.

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Supplementary material

Annex 1

Table S1 – Quality assessment of the cross-sectional studies using the STROBE scale (20)

		Autor, year															
		Gonzalo-Calvo, 2015	Wadley, 2015	Ulven, 2015	Stelzer, 2014	Abbasi, 2013	Draganidis, 2013;	Marklund, 2013;	Nieman, 2012;	Spiropoulos, 2010;	Stewart, 2007;	Fatouros, 2006;	Degerstrom, 2006;	Ostrowski, 1999;	Berneck er, 2011	Xiang, 2014;	Bonsignore, 2001;
STROBE scale Itens	1 (a)	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
	1 (b)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	×	✓	✓
	4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	6 (a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓
	7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓
	8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	9	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
	10	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

11	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12 (a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12 (b)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12 (c)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
12 (d)	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×
12 (e)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
13 (a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
13 (b)	✓	–	✓	✓	–	✓	–	–	–	–	–	–	–	✓	–	✓
13 (c)	✓	–	×	×	–	×	–	–	–	–	–	–	–	×	–	×
14 (a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
14 (b)	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
15	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
16 (a)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
16 (b)	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	✓	×	✓

16 (c)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
17	✓	✓	✓	✓	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
18	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
19	✓	×	✓	✓	✓	✓	×	×	×	×	×	×	×	✓	✓	✓
20	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
21	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
22	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	×	✓	✓	×	✓
Total	96.55%	92.59 %	90 %	89.66 %	92.59 %	86.21%	85.19%	88.89 %	85.19%	85.19 %	74.07%	81.48 %	77.78 %	79.31%	85.19 %	89.66 %

✓: yes; ×: no; —: not applicable; studies with a compliance percentage of the STROBE scale above 75% were considered to have good quality, studies with a compliance percentage between 50 and 75% were considered to have an average quality, studies with a compliance percentage below 50% were considered to have a low quality.

Annex 2

Table S2 - Quality assessment of the clinical trials using the CONSORT (19)

		Autor, year			
		Azizbeigi, 2015	Mucci, 1999B	Brenner, 1999	Connolly, 2004
CONSORT scale Itens	1 (a)	×	×	×	×
	1 (b)	✓	✓	✓	✓
	2 (a)	✓	✓	✓	✓
	2 (b)	✓	✓	✓	✓
	3 (a)	✓	✓	✓	×
	3 (b)	✓	–	–	–
	4 (a)	✓	✓	✓	✓
	4 (b)	✓	✓	✓	✓
	5	✓	✓	✓	✓
	6 (a)	✓	✓	✓	✓
	6 (b)	–	–	–	–
	7 (a)	✓	✓	✓	✓
	7 (b)	–	–	–	–
	8(a)	×	×	×	×
	8(b)	✓	×	×	×
	9	×	×	×	×
	10	×	×	×	×
	11 (a)	–	–	–	–
	11 (b)	–	–	–	–
	12(a)	✓	✓	✓	✓
	12(b)	✓	✓	✓	✓

13 (a)	—	—	—	—
13(b)	—	—	—	—
14 (a)	✓	✓	✓	✓
14(b)	—	—	—	—
15	✓	✓	×	✓
16	✓	✓	✓	✓
17 (a)	✓	✓	✓	✓
17 (b)	✓	✓	×	✓
18	✓	✓	✓	—
19	—	—	—	—
20	✓	✓	✓	✓
21	✓	✓	✓	✓
22	✓	✓	✓	✓
23	✓	✓	✓	✓
24	✓	—	—	✓
25	✓	✓	✓	✓
Total	86.66%	80.77%	73.08%	76.92%

✓: yes; ×: no; —: not applicable; studies with a compliance percentage of the STROBE scale above 75% were considered to have good quality, studies with a compliance percentage between 50 and 75% were considered to have an average quality, studies with a compliance percentage below 50% were considered to have a low quality.

Annex 3

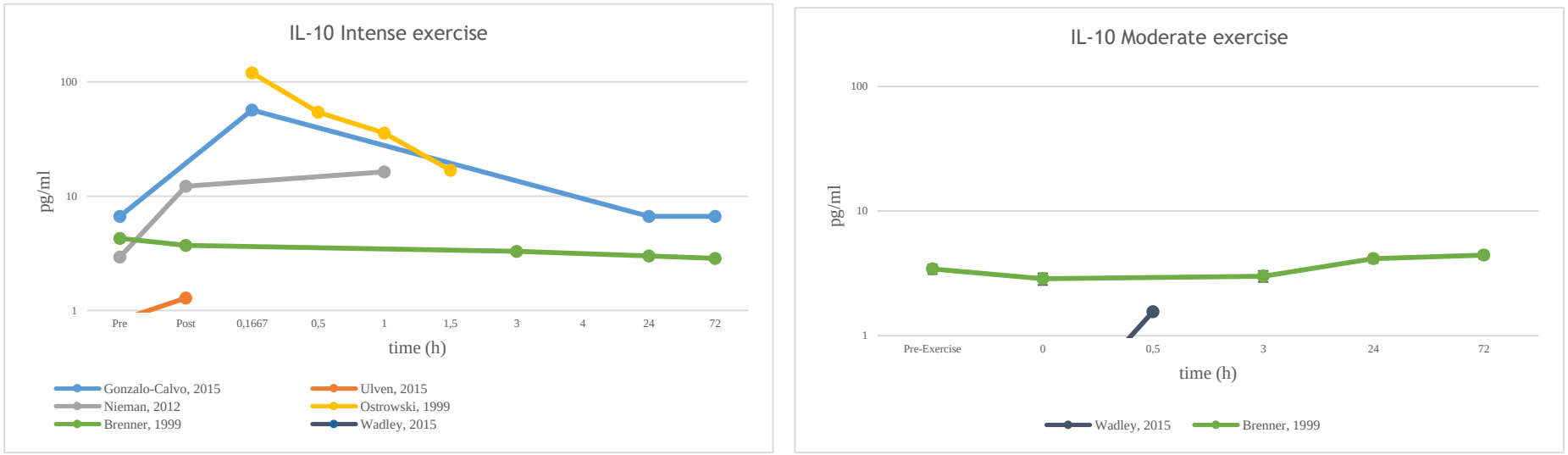
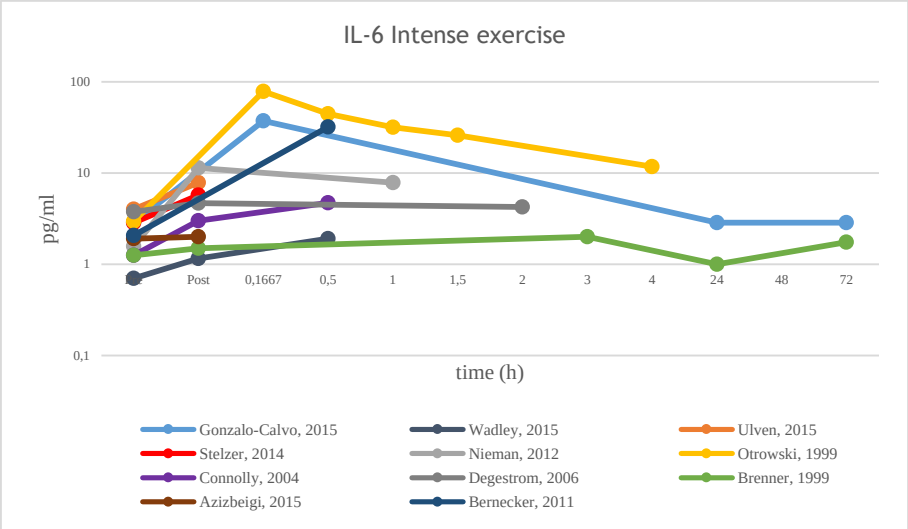


Figure S1 - IL-10 concentration with time, in different studies. Pre: before exercise; Post: immediately after exercise

Annex 4



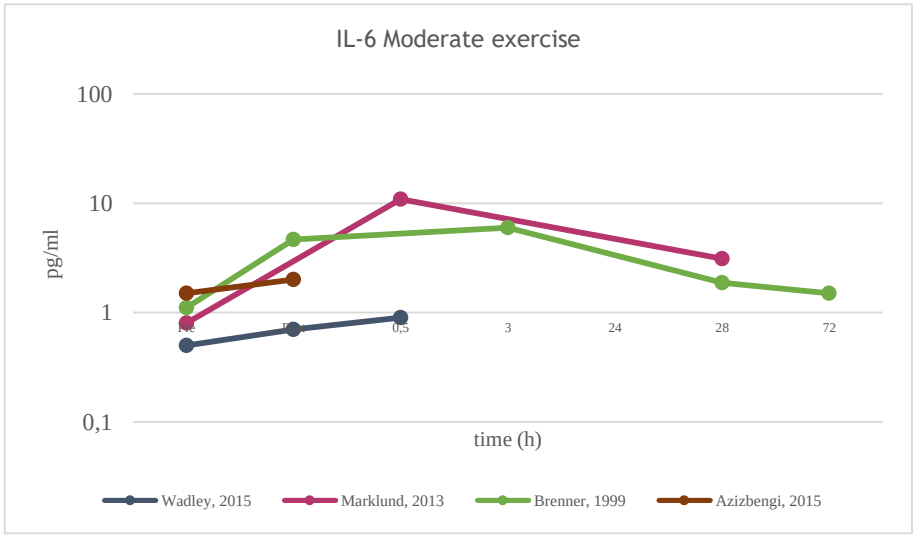


Figure S2 - IL-6 concentration with time, in different studies. Pre: before exercise; Post: immediately after exercise

Annex 5 – Scientific Divulgation

Scientific article submission

---------- Forwarded message ---------
De: <hannah@sportshealthjournal.org>
Date: terça, 8/01/2019 à(s) 12:59
Subject: Manuscript Submission
To: <olga@fcsaude.ubi.pt>
Cc: <olga@fcsaude.ubi.pt>

MS ID: SPORTSHEALTH/2019/033647
MS TITLE: Inflammatory effects of high and moderate intensity exercise - a Systematic Review

Dear Olga Lourenço,

This is to acknowledge receipt of your manuscript submission to Sports Health: A Multidisciplinary Approach. It will be reviewed by the Editorial Board and Reviewers' Panel. You will be apprised of the progress of this review.

As stated in our "Guidelines for Authors," a manuscript is reviewed only with the assurance that it is not under simultaneous consideration by another publication, nor has it been published elsewhere. If you have not already done so, please sign and return to the editorial office the Exclusive License (copyright) Agreement (https://submit.sportshealthjournal.org/journals/sportshealth/forms/copyright.pdf). Please be sure to indicate if this paper was, or will be presented at any scientific programs, either in part or entirely.

Please remember that you, as corresponding author, are responsible for keeping any co-author/s updated on the status of this manuscript. In addition, Sports Health has a 2-tier review process due to the multidisciplinary nature of the journal. Therefore, your paper will be handled by an editor in the field in which your paper falls, and approved by the editor-in-chief. Sometimes this results in multiple reviews, but please know that this ultimately results in the best possible manuscript for our entire readership.

Finally, please refer to this number SPORTSHEALTH/2019/033647 when you contact the Editorial Office with any questions.

Thank you for your submission to Sports Health!

Sincerely yours,

Edward M. Wojtys, MD
Editor

Abstract submission

1. Abstract:

The inflammatory effects in response to different exercise intensities: a systematic review

Érica Cerqueira[1], Daniel A. Marinho[2, 3], Henrique P. Neiva[2, 3], Olga Lourenço[1,4]

[1] FCS – UBI, Faculty of Health Sciences, University of Beira Interior

[2] Department of Sport Sciences, University of Beira Interior, Covilhã, Portugal

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[4] CICS – UBI, Health Sciences Research Centre, University of Beira Interior

ABSTRACT

Background: Exercise leads to a robust inflammatory response mainly characterized by the mobilization of leukocytes and an increase in circulating inflammatory mediators produced by immune cells and directly from the active muscle tissue. Both positive and negative effects on immune function and susceptibility to minor illnesses were observed. While engaging in moderate activity may enhance immune function above sedentary levels, excessive amounts of prolonged and high-intensity exercise may impair immune function. The goal of this systematic review was to clarify the inflammatory effects in response to different exercise intensities.

Methods: A systemic search examining exercise and inflammation was performed on PubMed and completed on July 31st, 2017. Eighteen articles were included, and their quality was assessed. The specific components that were examined included circulating blood levels of cytokines, leukocytes, creatine kinase (CK) and C-reactive protein (CRP).

Results: Most of the intervention studies showed changes in the assessed biomarkers, although these changes were not always consistent. White blood cells (WBC) had an increase immediately after intensive exercise (> 64 % VO_2max), without alteration after moderate exercise (46 - 64% VO_2max). The results suggested an elevation of the pro-inflammatory cytokines, namely IL-6, followed by an elevation of IL-10 that were more evident after intensive exercise bouts. CRP increased both after intense and moderate exercise, with peak increases up to 28h. CK increased only after intensive and long exercitation.

Conclusion: It is suggested a particularly caution due to increased susceptibility to illness when higher exercise intensities are used.

2. Abstract acceptance:

From: <eaaci2019abstract@eaaci.org>

Date: segunda, 11/03/2019 à(s) 17:07

Subject: EAACI Congress 2019: Notification of thematic poster presentation – Please confirm your attendance

To: <olga@fcsaude.ubi.pt>

European Academy of
Allergy and Clinical Immunology

Notification of thematic poster presentation

Olga Lourenco
Portugal

Dear Professor/Dr. Olga Lourenco,

On behalf of the Scientific Programme Committee we are pleased to inform you that your abstract has been accepted for presentation in a **Thematic Poster Session (TPS)** at the EAACI Congress 2019, to be held in Lisbon, Portugal, 01 - 05 June 2019.

Your abstract title: The Inflammatory Effects In Response To Different Exercise Intensities: A Systematic Review

Your abstract has been scheduled in the following session:

Session details
Session type: Thematic Poster Session (TPS)
Session number: TPS 06

Session title: Genetics, epigenetics and mechanisms
Session date: Sunday, 2 June 2019
Session time: 12:00 - 13:30
Session room: Thematic Poster Exhibition (on exhibition floor)

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The abstracts are organised in thematic groups of 15-20 posters and will be displayed for one day at E-Poster stations. At lunch time the presenters are required to stand by their station and answer questions from delegates. During this time, two moderators will also visit each station and ask the presenters to briefly present their findings. Please note that each TPS runs for 90 minutes in total.

E-Posters have to be uploaded prior to the presentation in order to allow technical processing. You will be sent further instructions in April 2019. E-Posters will be also available for viewing in the EAACI Congress App as of 01 June 2019 and onsite at the congress in the Virtual Congress Hubs.

The following information will be sent to you closer to the Congress:
- Final Abstract number (appears in Final Programme)
- Guidelines for the preparation of your poster and other practical details
- Schedule and guidelines for uploading your electronic posters

Confirmation of your presentation
Please note that **only the presenting author** will receive e-mails concerning the abstract **and is responsible for informing the corresponding author and all co-authors of the status of the abstract.**

All presenting authors must confirm their attendance no later than 15 March 2019. To confirm your presentation, please click on the link below to log in to the presentation confirmation page and follow the instructions shown.

Click here: http://scientific.eaaci.org/eaaci2019
User name: olga@fcsaude.ubi.pt

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Publication in the online edition of the Allergy Journal: abstracts that are presented at the Congress, will be published in the online edition of the Allergy Journal after the Congress. If you fail to present your abstract at the Congress, it will not be published.

By confirming the presentation of your abstract, you grant permission to the organisers to publish the abstract on the Congress website and in the online edition of the Allergy Journal.

Best presentation prize
A prize of EUR 200 will be awarded to the best presentation in each abstract session. The winners of the awards will be acknowledged on the Congress website. The prize money will be paid after the Congress and a diploma will be sent by e-mail.

Visa requirements
For some nationalities a visa is required to enter Portugal. We strongly advise you to investigate the visa requirements that apply to your nationality and, when necessary, make arrangements accordingly.
Invitation letters can be requested during the registration process. EAACI cannot be made responsible for not granted visas.

Hotel reservations
To stay at a prime location close to the Congress venue, it is recommended to book your hotel now. June is a busy season in Lisbon and hotels are already becoming fully booked.
For further information and to make your reservation, please **click here**.
K.I.T. Group is the official EAACI housing agent. Be aware of fraudulent groups acting as housing agents.

Please do not hesitate to contact us if you have questions or need further information.

We look forward to seeing you in Lisbon in June.

Yours sincerely,

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