

ΑΝΑΣΚΟΠΗΣΗ REVIEW

Η άσκηση ως θεραπεία στη ρευματοειδή αρθρίτιδα.

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ΠΕΡΙΛΗΨΗ

Αποτελέσματα συλλογικών ερευνών αποκαλύπτουν σημαντικές ευεργετικές επιδράσεις της σωματικής δραστηριότητας σε διαφορετικές παραμέτρους υγείας ασθενών με Ρευματοειδή

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Αρθρίτιδα (ΡΑ). Ωστόσο, οι ασθενείς με ΡΑ παραμένουν σωματικά αδρανείς, το οποίο οφείλεται σε παράγοντες που αφορούν τόσο τον ασθενή όσο και τον επαγγελματία υγείας. Στην παρούσα βιβλιογραφική ανασκόπηση, περιγράφουμε τις ευεργετικές φυσιολογικές επιδράσεις της φυσικής δραστηριότητας στη ΡΑ και διερευνούμε τους πιθανούς λόγους για τους οποίους ασθενείς με ρευματοειδή αρθρίτιδα εξακολουθούν να παραμένουν σωματικά αδρανείς.

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Λέξεις-Κλειδιά: Ρευματοειδής αρθρίτιδα, άσκηση, θεραπεία

Exercise as medicine in rheumatoid arthritis.

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ABSTRACT

Collective research evidence reveals a beneficial impact of physical activity on a number of different health outcomes in patients with Rheumatoid Arthritis (RA). However, RA patients still remain physically inactive due to factors involving both the patient and the health professional. In this review, we describe the beneficial effects of physical activity in RA and we explore the potential reasons why RA patients still remain physically inactive by a) investigating whether current provision for incorporating physical activity in clinical management is adequate/sufficient and b) discussing evidence from both from the patients' and healthcare providers' perspectives as to why RA patients still remain physically active.

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INTRODUCTION

Rheumatoid arthritis (RA) is a disabling form of systemic inflammatory arthritis that has a prevalence of ~1%¹ and is characterized by long-term inflammation, pain, and fatigue; therefore, increased functional disability and joint damage. With no known cure, the current treatment strategies for RA focus on reducing pain, minimize symptoms and potentially prevent further disease progression. Rheumatoid arthritis is, however, a debilitating disease not only for its disease-related symptoms but also its accompanying systemic manifestations. The predominant of these manifestations is an increased risk for cardiovascular disease (CVD). Moreover, RA also influences psychological wellbeing, with a recent meta-analysis revealing that ~40% of RA patients suffer from depression.² As such, it seems that this disease affects the health of individuals at multiple levels, and thus, relevant interventions that address and improve these health outcomes are warranted.

Physical Activity in Rheumatoid Arthritis

Physical activity is any bodily movement produced by skeletal muscles that result in energy expenditure above resting levels; whereas exercise is a planned, structured and repetitive physical activity. The World Health Organization³ has identified physical inactivity as the 4th leading cause of overall mortality in adults. However, data reveals that the majority of the adult population still remain physically inactive.³ At present, the guidelines for physical activity state that adults need to engage in physical activity for at least 150 minutes/week of moderate-intensity, at least 75 minutes/week of vigorous-intensity or some combination of the two intensities.⁴ These cut-off points have been shown to result in beneficial physiological and psychological adaptations that may improve health. These levels of physical activity are evidently difficult to achieve for the majority of the adult population due to a range of barriers mainly pertaining to perception of time and/or lack of motivation. Patients with chronic musculoskeletal diseases such as RA⁵ may be even more physically inactive compared to the normal population, as disease-related symptoms may further hinder the participation in physical activity. However, increasing physical activity and/or exercise (i.e., structured physical activity aimed at improving a specific characteristic of fitness, such as cardiorespiratory fitness) is indeed an intervention that impacts positively on the most important clinical and systemic manifestations in patients with RA.

Disease-Related Symptoms

Data demonstrate clearly that physical activity is an intervention that should be utilised in the management of RA,⁶ and currently in the literature there is no single report demonstrating exacerbation of RA-

related symptoms as a result of even high-intensity physical activity.^{7, 8} In line with this, two Cochrane systematic reviews and meta-analyses confirm that the combination of aerobic and resistance training in RA improves functional outcomes potentially via blunting the inflammatory response.^{9,10} At present, there are no systematic reviews and meta-analyses examining the effects of physical activity on inflammatory biomarker changes in RA; however, in low-grade inflammatory conditions such as diabetes mellitus, such studies demonstrate an effect of exercise on reducing two biomarkers overexpressed in RA, C-reactive protein (CRP, a biomarker of hepatic origin and the most frequently studied biomarker of inflammatory response) and the pro-inflammatory cytokine interleukin 6 (IL-6).¹¹ The potential role of physical activity on the inflammatory response is also supported by large population cohorts, such as the British Regional Heart study, the Third National Health and Nutrition Examination Survey (NHANESIII), the Cardiovascular Health study (CHS), as well as the Health ABC study, all of which revealed an inverse and independent dose-response association between CRP concentration and level of physical activity, which may be a physiological mechanism mediated by exercise-induced reductions in adiposity levels.¹² Indeed, in RA, reductions in adiposity have been shown to associate with reductions in CRP after a six-month individualized moderate-intensity combined aerobic and resistance exercise program.¹³ Although the exact physiological mechanisms by which physical activity ameliorates inflammation in RA have not been studied *per se*, in the general population, exercise induces physiological adaptations that result in marked improvements in inflammatory status as well as muscle function via reductions in systemic immune cell production of inflammatory proteins that occur locally in the muscle. In adults at high risk of CVD, similarly to RA, physical activity reduces mononuclear cell production of cytokines related to atherogenesis (specifically, tumor necrosis factor alpha [TNF α] and Interleukin 1 [IL-1]), but increases the expression of atheroprotective cytokines (such as Interleukins 10 and 4 [IL-10 and IL-4] and transforming growth factor beta 1 [TGF β 1]).¹⁴ Moreover, contractile properties of the muscle include production of myokines, specifically IL-6, which increases hundred-fold in response to exercise. However, exercise-induced IL-6 has anti-inflammatory properties rather than inflammatory, via stimulating the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist.¹⁵ Specifically, IL-6 produced in response to skeletal muscle contractions may upregulate free fatty acid metabolism via its lipolytic activities but also may upregulate glucose homeostasis by affecting hepatic glucose production and/or muscle glucose utilization.¹⁶ Although these

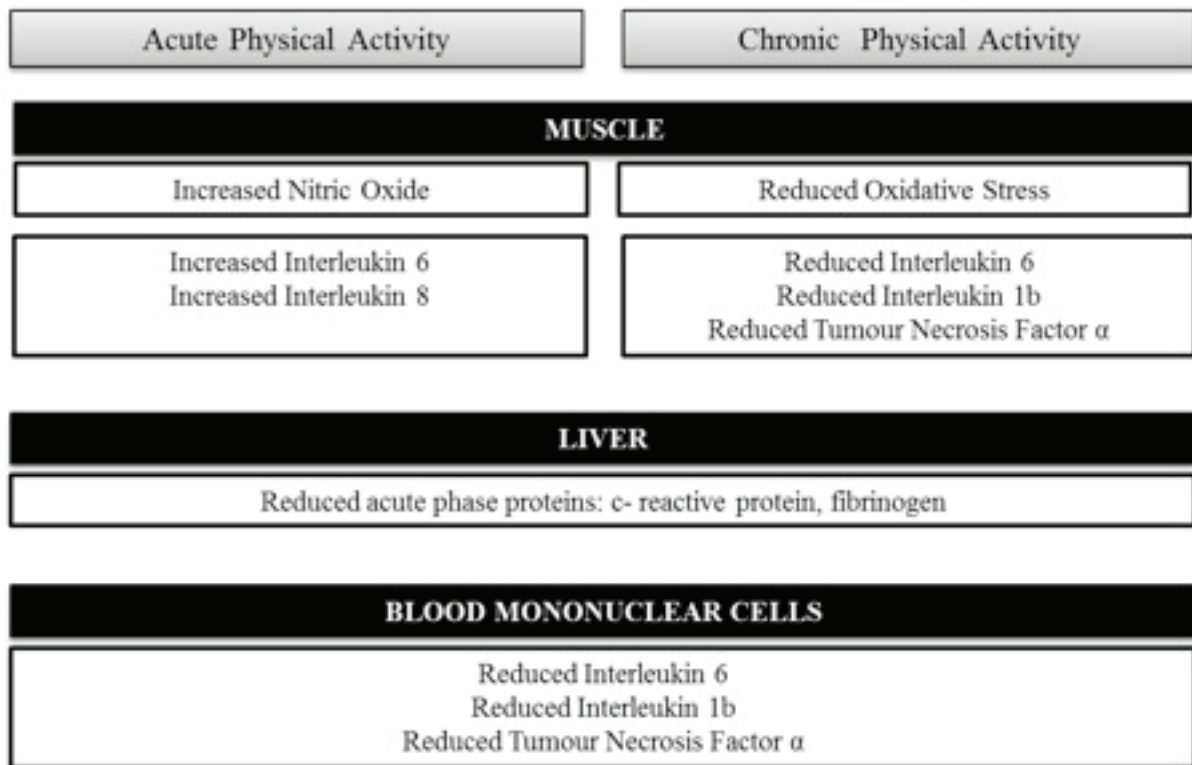


Figure 1. Suggested effects of exercise on inflammatory responses.

adaptations may favourably impact on the overall inflammatory responses, long-term engagement in exercise programmes may also improve modulation of intracellular signalling pathways as well as cellular function that are mediated by nitric oxide and reactive oxygen species¹² eventually alleviating inflammation. Indeed, in RA, two recent studies pertaining to the same trial, revealed that tailored exercise leads to significant improvement in specific oxidative stress mechanisms as well as improving measurements related to nitric oxide production.^{17, 18} It is necessary that these mechanisms are better understood in relevant trials, however, the overall evidence suggests an exercise-induced anti-inflammatory effect via the mechanisms highlighted in Figure 1.

Cardiovascular Disease Outcomes

A meta-analysis of observational studies reveals that RA patients suffer from an increased risk of cardiovascular mortality¹⁹. This may be due to the increased prevalence of individual CVD risk factors; specifically dyslipidemia,^{20,21} insulin resistance,^{22,23} hypertension,^{24,25} obesity,^{26,27} potential vascular dysfunction^{28,29} as well as chronic inflammation, which independently associates with cardiovascular mortality and morbidity.^{30,31} In contrast, higher physical activity in RA associates with a significantly better

cardiovascular profile in RA patients, and in specific an improvement in both classical (adiposity, systolic blood pressure, insulin resistance and total cholesterol) and novel (fibrinogen, homocysteine, c-reactive protein, von Willebrand factor) CVD risk factors.³² Moreover, a recent trial revealed that RA patients that embark on a six month aerobic and resistance exercise programme experience significant improvements in CVD classical risk factors (lipid profiles, systolic blood pressure and adiposity), specific biomarkers of oxidative stress, micro- and macro-vascular function, and overall 10-year CVD risk in exercising RA patients compared to RA controls.^{13,17,18} The exact physiological mechanisms by which these beneficial adaptations occur remain elusive and thus, more research is required in this field. However, the above results are in line with results from relevant meta-analyses for the general population demonstrating beneficial effects of physical activity on systolic blood pressure,³³ lipid profiles,³⁴ insulin sensitivity³⁵ as well as adiposity.³⁶

Sedentary Behavior in Rheumatoid Arthritis

Sedentary behavior can be defined as any waking behavior characterized by energy expenditure no greater than 1.5 metabolic equivalents of task (METs) while in a sitting or reclining posture.³⁷ This definition helps to distinguish individuals who are “physically inactive”;

that is, individuals who are performing insufficient amounts of moderate-to-vigorous physical activity to meet recommended physical activity guidelines, from those who are engaged in large amounts of sedentary behavior.³⁷ This is useful because it is possible for a person to meet recommended physical activity guidelines (e.g., 30 minutes of moderate physical activity per day), while engaging in sedentary behaviors for long periods of time (e.g., working sitting at a desk for several hours).

Cumulative research suggests a negative dose-dependent relationship of sedentary behavior with mortality from all causes, cardiovascular disease and cancer, while better cardiorespiratory fitness shows the exact opposite trends.^{38,39} Specifically for RA, cardiorespiratory fitness has been found to strongly and inversely associate with CVD risk factors and markers of inflammation;⁴⁰ however, currently there is a dearth of data with regards to sedentary behaviors and their associations with CVD risk factors as well as disease-related manifestations. Relevant research is required in this field to investigate how sedentary behaviors impact on RA disease and systemic manifestations.

Is exercise incorporated in the clinical management of Rheumatoid Arthritis?

Given the strong evidence, at least for disease-related symptoms, that is available for RA, it would be reasonable to suggest that physical activity would be actively incorporated in the clinical management of RA patients. As such, as part of this paper, we have gathered the most important official guidelines for patients with RA, in order to investigate the information provided for the utilization of physical activity and/or exercise in the clinical management of RA. The following resources for the management of RA were investigated and the information provided appears below.

European League Against Rheumatism recommendations

The European League Against Rheumatism (EULAR) recommendations for patient education for people with inflammatory arthritis suggests that patient education in combination with physical therapy/joint protection exercises or physical activity has positive influences on physical function and activity, reduces pain and improves health status. However, no specific recommendations were discussed or specific mention was brought forward for physical activity and/or exercise. In the same manuscript, it is acknowledged that patients' needs and expectations are wide about physical exercises without further supporting evidence on this matter. Finally, it is recommended that physical exercise programs could be possible and could be provided with the addition of educational group

sessions to be more effective. However, a study in RA has shown that although RA patients' education/awareness about healthy lifestyles can improve as a result of an educational intervention program, the actual behavior does not improve (i.e. patients are more aware but this does not make them eat healthier or exercise more).⁴¹

Moreover, the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis reported nothing about physical activity and/or exercise. Finally, in the EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis, it is mentioned that exercise, as a lifestyle modification, should be provided to all patients with chronic inflammatory arthritis since it may improve CVD risk, however, no specific suggestions were explored.

British National Institute for Health and Care Excellence guidance

In the British National Institute for Health and Care Excellence (NICE) guidance for RA, in the subsection for the multidisciplinary team in section 1.1 (Referral, diagnosis and investigations), it is mentioned that patients with RA should have access to specialist physiotherapy to improve general fitness and be encouraged to do regular exercise, as well as doing exercise to enhance joint flexibility, muscle strength and for managing other functional impairments. There is no mention of exercise and/or physical activity in section 4 (Implementation) or any other section.

Arthritis Research United Kingdom

The official website of Arthritis Research United Kingdom has a dedicated webpage for all Arthritis diseases combined, but not RA specifically; although the information provided refers – in places – to exercise instructions specifically for patients with “hot” or “swollen” joints. This manuscript in general, describes stretching, strength and fitness exercises. Five to ten sets of stretching exercises are recommended (although no specific information is provided for muscle groups) up to the range of motion that does not exacerbate pain, while holding the stretch for 5-10sec; for patients with “hot” or “swollen” joints, gentle stretching is also recommended one a day of a few repetitions. For strength, general advice is offered on performing these exercises slowly and with to start with a low number of repetition but progress gradually (no specific information is given on muscle groups/repetitions). Specific mention to Pilates training is provided, whereas for patients with “hot” or “swollen” joints, is it recommended to avoid strength training until the joint is back to normal: when this is the case, the exercises should be performed

gently and with a low number of repetitions. Finally, for fitness exercises, general information is provided for swimming, walking, fitness classes, cycling and joining a gym, whereas there is no information for patients with “hot” or “swollen” joints. The information provided by the Arthritis Research United Kingdom, refers patients very often to seek advice from a physiotherapist about all the above exercises.

American College of Rheumatology guidelines

The American College of Rheumatology guidelines documents are only specific to drug updates and recommendations.

The European Musculoskeletal Conditions Surveillance and Information Network

The European Musculoskeletal Conditions Surveillance and Information Network (EUMUSC.net) is a project aiming to raise and harmonize quality of care for rheumatic diseases and musculoskeletal health in specific European countries, and provides an official document for Standards of Care in RA. This document indeed recommends physical activity and/or exercise as part of lifestyle advice, as well as for rehabilitative purposes for this population. In specific, it suggests that RA patients should be educated (on the positive effects) and receive professional advice for exercise in order to improve cardiovascular health and prevent muscle wasting, a common characteristic in RA. In addition, it has a comprehensive analysis of the exercises that can be utilized in the management of RA, however, it suggests that the exercise programmes should be prescribed and supervised by qualified practitioners whereas, it also suggests that the exercise regime should commence with low-intensity exercise. Furthermore, it recommends a breakdown of the program in aerobic (1-3 times per week) and resistance components, however, the recommendations of the latter do not seem to be in line with the available literature. In specific, the suggestions pertain to a once-a-week resistance program consisting of exercises for all major muscle groups, with exercises that last for 30 seconds of contracting a muscle group following 30 seconds of relaxation. In contrast, different comprehensive reviews and meta-analyses in this field, suggest that moderate intensity resistance exercise using standard equipment is safe and significantly improves RA-related manifestations without exacerbating disease symptoms.^{7,9}

It appears that there is no consistent provision from the most important European and American resources for incorporating physical activity in managing RA. The EUMUSC.net provided the most detailed guidance, with sufficient information for incorporating physical activity in the management of RA, although more

conservative advice was given for resistance exercise. The Arthritis Research United Kingdom also provided very general information which is mainly relevant to arthritis patients, rather than RA.

At present, there is no recent data revealing whether physical activity is indeed utilized or recommended by clinicians in the clinical management of RA. From the available data, however, it seems that patients with RA have still worrying low levels of both cardiorespiratory fitness and physical activity, with the latter remaining unchanged in the last two decades.^{40,42,43} The potential reasons for these low levels of fitness and activity can be explored by presenting data from the perspective of the patient and the health practitioner separately.

Patient perspective

The most recent systematic review in this field concluded again that physical activity levels are still low in RA and has highlighted that disease-related characteristics such as pain and fatigue are commonly reported barriers by RA patients for not engaging in physical activity; interestingly RA patients who are sufficiently physically active report the same barriers as those who are not active but appear to be more capable of overcoming them.⁵ Even in countries with excellent educational programmes, RA patients remain physically inactive despite knowing the beneficial effects of exercise,⁴⁴ which confirms earlier findings that improving knowledge/awareness may not be sufficient alone to change behavior towards being more active.⁴¹ Importantly, lack of trust in exercise professionals may also be an important factor promoting inactive behaviors, since the approach to exercise prescription for RA patients should not be universal and should be based on the patient's functional abilities and preferences.⁶

Health Professionals perspective

For a long time health professionals have been advising rest rather than exercise for managing RA, due to the fear that exercise may exacerbate disease symptoms.^{5,7} In addition, there is no current provision to train exercise health professionals in order to have specific knowledge to develop tailored exercise prescriptions for RA patients, which has to be developed based on the individual's functional abilities.⁴⁵ These two factors may further contribute to physical inactivity and increased sedentary behavior observed in RA studies. We have previously and recently proposed a pragmatic approach in developing tailored exercise programmes in RA patients, using an adopted model of cardiac rehabilitation.^{6,46} In brief, based on a) baseline assessments that are used to determine the intensity of the programme, b) patient's history and functional limitations, c) patients exercise preferences and d) RA-

specific trained exercise personnel (when the exercise programme is conducted in a supervised environment), the development of an exercise programme can have significant different effects on multiple different health factors, including improved disease symptoms and cardiovascular profile.^{13,17} Similar approaches have been utilised with similar results by other researchers.^{47,48} Facilitating long-term adherence to physical activity may also be challenging for RA patients, but developing self-autonomous exercising patients and monitoring improvements using specific patient selected outcomes (e.g., weight, fitness) – as per the UK National Institute for Health and Care Excellence (NICE) guidelines – may help achieve this.

CONCLUSION

For more than two decades, patients with RA have reported low levels of physical activity, despite the convincing evidence that physical activity has important benefits in terms of both disease-related and systemic manifestations of the disease. Lack of a universal approach and relevant provision from official guidelines, patient specific barriers as well as lack of knowledge from health professionals may contribute to the low levels of physical activity and subsequent low cardiorespiratory fitness observed. Relevant studies are necessary in this field to identify ways of supporting an increase in physical activity levels in RA patients using behavioral change theoretical models.

References

1. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford)* 2002; 41: 793-800.
2. Matcham FL, Rayner S, Steer M, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2013; 52: 2136-48.
3. W.H.O., *World Health Organisation. Physical activity.* <http://www.who.int/mediacentre/factsheets/fs385/en/>. 2015.
4. BHF, British Heart Foundation. Economic cost of physical inactivity Accessed: 15/02/2015; <http://www.bhfactive.org.uk/userfiles/Documents/economiccosts.pdf>. 2015.
5. Veldhuijzen van Zanten JJ, Rouse PC, Hale ED, Ntoumanis N, Metsios GS, Duda JL, et al. Perceived Barriers, Facilitators and Benefits for Regular Physical Activity and Exercise in Patients with Rheumatoid Arthritis: A Review of the Literature. *Sports Med* 2015 Jul 29. [Epub ahead of print]
6. Metsios GS, Stavropoulos-Kalinoglou A, Kitas GD. The role of exercise in the management of rheumatoid arthritis. *Expert Rev Clin Immunol* 2015; 17:1-10.
7. Lemmey AB. Efficacy of progressive resistance training for patients with rheumatoid arthritis and recommendations regarding its prescription. *Int J Clin Rheumatol* 2011; 6:189-205.
8. Metsios GS, Lemmey A. Exercise as Medicine in Rheumatoid Arthritis: Effects on Function, Body Composition, and Cardiovascular Disease Risk. *Journal of Clinical Exercise Physiology* 2015; 4: 14-22.
9. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev* 2009; 4:CD006853.
10. Van Den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000; 2:CD000322.
11. Hayashino Y, Jackson JL, Hirata T, Fukumori N, Nakamura F, Fukuhara S, et al. Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Metabolism* 2014; 63: 431-40.
12. Nicklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. *Exerc Sport Sci Rev* 2009; 37: 165-70.
13. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013; 72:1819-25.
14. Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA* 1999; 281:1722-7.
15. Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. *J Appl Physiol* (1985) 2007; 103: 1093-8.
16. Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. *FASEB J*. 2003; 17(8): p. 884-6.
17. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Nightingale P, Sandoo A, Dimitroulas T, et al. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014; 73:748-51.
18. Wadley AJ, Veldhuijzen van Zanten JJ, Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Kitas GD, et al. Three

- months of moderate-intensity exercise reduced plasma 3-nitrotyrosine in rheumatoid arthritis patients. *Eur J Appl Physiol* 2014; 114:1483-92.
19. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008 ; 59: 1690-7.
 20. Toms TE, Panoulas VF, Douglas KM, Griffiths H, Sattar N, Smith JP, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? *Ann Rheum Dis* 2010; 69: 683-8.
 21. Toms TE, Panoulas VF, Smith JP, Douglas KM, Metsios GS, Stavropoulos-Kalinoglou A, et al. Rheumatoid arthritis susceptibility genes associate with lipid levels in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 1025-32.
 22. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. *Arthritis Rheum* 2006; 54:2765-75.
 23. Dessein PH, Joffe BI, Stanwix AE. Inflammation, insulin resistance, and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. *J Rheumatol* 2003; 30: 1403-5.
 24. Panoulas VF, Douglas KM, Smith JP, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, et al. Transforming growth factor-beta1 869T/C, but not interleukin-6 -174G/C, polymorphism associates with hypertension in rheumatoid arthritis. *Rheumatology (Oxford)* 2009; 48:113-8.
 25. Panoulas VF, Metsios GS, Pace AV, John H, Treharne GJ, Banks MJ, et al. Hypertension in rheumatoid arthritis. *Rheumatology (Oxford)*. 2008; 47: 1286-98.
 26. Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF, Douglas KM, Nevill AM, Jamurtas AZ, et al. Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68:242-5
 27. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KM, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. *Int J Obes (Lond)* 2010; 34:295-301.
 28. Sandoo A, Carroll D, Metsios GS, Kitas GD, Veldhuijzen van Zanten JJ. The association between microvascular and macrovascular endothelial function in patients with rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther* 2011; 13:R99.
 29. Sandoo A, Veldhuijzen van Zanten JJ, Metsios GS, Carroll D, Kitas GD. Vascular function and morphology in rheumatoid arthritis: a systematic review. *Rheumatology (Oxford)* 2011; 50:2125-39.
 30. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. *Arthritis Rheum* 2005; 52: 2293-9.
 31. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005; 52: 722-32.
 32. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Wilson M, Nevill AM, Koutedakis Y, et al. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 188-94.
 33. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2013; 2: e004473.
 34. Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med* 2007; 167: 999-1008.
 35. Conn VS, Koopman RJ, Ruppert TM, Phillips LJ, Mehr DR, Hafidahl AR, et al. Insulin Sensitivity Following Exercise Interventions: Systematic Review and Meta-Analysis of Outcomes Among Healthy Adults. *J Prim Care Community Health* 2014; 5:211-222.
 36. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PLoS One* 2013; 8: e56415.
 37. Sedentary Behavior Research, N., Letter to the editor: standardized use of the terms “sedentary” and “sedentary behaviors”. *Appl Physiol Nutr Metab* 2012; 37: 540-2.
 38. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009; 41:998-1005.
 39. Vigen R, Ayers C, Willis B, DeFina L, Berry DJ, Association of cardiorespiratory fitness with total, cardiovascular, and noncardiovascular mortality across 3 decades of follow-up in men and women. *Circ Cardiovasc Qual Outcomes* 2012; 5:358-64.
 40. Metsios GS, Koutedakis Y, Veldhuijzen van Zanten JJ, Stavropoulos-Kalinoglou A, Vitalis P, Duda JL, et al. Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study . *Rheumatology (Oxford)* 2015; in press (DOI: kev035).
 41. John H, Hale ED, Treharne GJ, Kitas GD, Carroll D. A randomized controlled trial of a cognitive behavioral patient education intervention vs a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease. *Rheumatology (Oxford)* 2013; 52: 81-90.
 42. Stenstrom CH, Lindell B, Swanberg E, K. Harms-Ringdahl K, Nordemar R. Functional and psychosocial consequences of disease and experience of pain and exertion in a group of rheumatic patients considered for active training. Result of a survey in Bollnas Medical District. I. *Scand J Rheumatol* 1990; 19: 374-82.
 43. Yu CA, Rouse PC, Veldhuijzen Van Zanten JJ, Ntoumanis N, Kitas GD, Duda JL, et al. Subjective and objective levels of physical activity and their association with cardiorespiratory fitness in rheumatoid arthritis patients. *Arthritis Res Ther* 2015; 17: 59.
 44. Makelainen P, Vehvilainen-Julkunen K, Pietila AM. Rheumatoid arthritis patients' knowledge of the disease and its treatments: a descriptive study. *Musculoskeletal Care* 2009; 7: 31-44.
 45. Wilcox S, Der Ananian C, Abbott J, Vrazel J, Ramsey C, Sharpe PA, et al. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Rheum* 2006; 55:616-27.
 46. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Treharne GJ, Panoulas VF, Douglas KM, et al., Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. *Rheumatology (Oxford)* 2008; 47:239-48.
 47. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis Rheum* 2003; 48:2415-24.
 48. Munneke M, de Jong Z, Zwinderman AH, Ronday HK, van Schaardenburg D, Dijkmans BA, et al. Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. *Arthritis Rheum* 2005; 53: 410-7.