The role of physical activity in individuals with cardiovascular risk factors: an opinion paper from Italian Society of Cardiology-Emilia Romagna-Marche and SIC-Sport

Milena Nasi\textsuperscript{a}, Giampiero Patrizi\textsuperscript{b}, Carmine Pizzi\textsuperscript{c}, Matteo Landolfo\textsuperscript{d}, Giuseppe Boriani\textsuperscript{e}, Alessandra Dei Cas\textsuperscript{f}, Arrigo F.G. Cicero\textsuperscript{d}, Federica Fogacci\textsuperscript{d}, Claudio Ravezzani\textsuperscript{c}, Giovanbattista Sisca\textsuperscript{g,h}, Alessandro Capucci\textsuperscript{i}, Marco Vitolo\textsuperscript{e}, Nazzareno Galie\textsuperscript{c}, Claudio Borghi\textsuperscript{d}, Umberto Berrettini\textsuperscript{j}, Massimo Piepoli\textsuperscript{k} and Anna V. Mattioli\textsuperscript{a}

Regular physical activity is a cornerstone in the prevention and treatment of atherosclerotic cardiovascular disease (CVD) due to its positive effects in reducing several cardiovascular risk factors. Current guidelines on CVD suggest for healthy adults to perform at least 150 min/week of moderate intensity or 75 min/week of vigorous intensity aerobic physical activity. The current review explores the effects of physical activity on some risk factors, specifically: diabetes, dyslipidemia, hypertension and hyperuricemia. Physical activity induces an improvement in insulin sensitivity and in glucose control independently of weight loss, which may further contribute to ameliorate both diabetes-associated defects. The benefits of adherence to physical activity have recently proven to extend beyond surrogate markers of metabolic syndrome and diabetes by reducing hard endpoints such as mortality. In recent years, obesity has greatly increased in all countries. Weight losses in these patients have been associated with improvements in many cardiometabolic risk factors. Strategies against obesity included caloric restriction, however greater results have been obtained with association of diet and physical activity. Similarly, the beneficial effect of training on blood pressure via its action on sympathetic activity and on other factors such as improvement of endothelial function and reduction of oxidative stress can have played a role in preventing hypertension development in active subjects. The main international guidelines on prevention of CVD suggest to encourage and to increase physical activity to improve lipid pattern, hypertension and others cardiovascular risk factor. An active action is required to the National Society of Cardiology together with the Italian Society of Sports Cardiology to improve the prescription of organized physical activity in patients with CVD and/or cardiovascular risk factors.

J Cardiovasc Med 2019, 20:631–639

Keywords: cardiovascular risk factors, diabetes, hypertension, physical activity, uric acid

\textsuperscript{a}Department of Surgical, Medical and Dental Department of Morphological Sciences Related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, \textsuperscript{b}Department of Cardiology, Carpi Hospital, Carpi, \textsuperscript{c}Department of Experimental, Diagnostic and Specialty Medicine-DIMES, Alma Mater Studium, \textsuperscript{d}Department of Medicine and Surgery Sciences, University of Bologna, Bologna, \textsuperscript{e}Division of Cardiology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, \textsuperscript{f}Endocrinology and Metabolism, Department of Clinical and Experimental Medicine, University of Parma, Parma, \textsuperscript{g}Bologna F.C., \textsuperscript{h}FIFA Medical Centre of Excellence, Isokinetic Medical Group, Bologna, Marche Polytechnic University, Ancona, \textsuperscript{i}Department of Cardiology, Camerino-Hospital, Camerino and \textsuperscript{j}Heart Failure Unit, Cardiology, Guglielmo da Saliceto Hospital, Piacenza, Italy

Correspondence to Anna V. Mattioli, MD, Associate Professor of Cardiovascular Diseases, Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Via del Pozzo, 71-41124 Modena, Italy
Tel: +39 0594224043; fax: +39 0594223229; e-mail: annavittoria.mattioli@unimore.it

Received 20 December 2018 Revised 18 March 2019 Accepted 13 July 2019

\textsuperscript{1}© 2019 Italian Federation of Cardiology - I.F.C. All rights reserved.

Introduction

Physical activity is defined as any body movement that increases oxygen consumption and can be performed during work or during leisure activities. On the contrary exercise is defined as the physical activity that improves health or gains performance benefits.\textsuperscript{1}

Several studies demonstrated that regular physical activity reduces rates of all-cause mortality, cardiovascular disease (CVD), hypertension, stroke, metabolic syndrome, type 2 diabetes (T2D) as well as of other chronic medical conditions.\textsuperscript{2} Regular physical activity is a cornerstone in the prevention and treatment of atherosclerotic CVD due to its positive effects in reducing SBP/DBP, body weight, blood glucose, triglycerides, LDL cholesterol (LDL-C) and in improving HDL cholesterol (HDL-C).\textsuperscript{3} Conversely, according to the WHO, physical inactivity is the fourth leading risk factor for global mortality and its prevalence can be compared with all other cardiovascular risk factors; consequently exercise and regular physical activity are recommended for both primary and secondary prevention of CVD\textsuperscript{2–4} (Table 1).
Current guidelines on CVD suggest for healthy adults of all ages to perform at least 150 min/week of moderate intensity or 75 min/week of vigorous intensity aerobic physical activity or an equivalent combination thereof; for additional benefits in healthy adults, a gradual increase in aerobic physical activity to 300 min/week of moderate intensity, or 150 min/week of vigorous intensity aerobic physical activity, or an equivalent combination thereof is recommended. The aim of this review is to analyse the effects of regular physical activity and exercise on the cardiovascular risk factors.

**The dose of physical activity ‘something is better than nothing’**

As mentioned before current international guidelines generally recommend 150 min/week of moderate to vigorous physical activity. Despite several studies were conducted in the attempt to assess the minimal and optimal dosage of physical activity, this still remains an open issue. Wen et al. demonstrated that even a lower amount of exercise (15 min a day or 90 min a week of moderate-intensity exercise) than the recommended 150 min a week could result in healthy benefits irrespective of age, sex and CVD risk. Nevertheless the lower and upper limit of aerobic physical activity intensity, duration and frequency to exert a beneficial effect are still unknown. In fact, despite the proven benefits of physical activity, extreme exercise may increase risk of cardiovascular events although this matter remains controversial and the risk of an adverse cardiovascular events although this matter remains unknown.

**Effects of physical activity on endothelial dysfunction**

The onset of CVDs is mediated by vascular damage that lead to atherogenesis and plaque formation. One of the most important and earliest events that prime vascular events although this matter remains controversial and the risk of atherogenic state, by an increased smooth muscle proliferation and vascular inflammation. Endothelial cells have a role in the inhibition of the aggregation of platelets, oxidative stress, VSMCs, recruiting of leukocytes and leukocyte adhesion. Its deficiencies may be the first manifestation of endothelial dysfunction in the absence of modifications in the structure of the vessel wall.

NO reduction is a consequence of oxidative stress in the endothelial cells that is associated with an increased risk of endothelial dysfunction and to inflammation that alters the capacity of vessels to respond to endotherm-dependent vasodilators and vasoconstrictors. Product from damaged endothelial cells and oxidative stress activate NLRP3 inflammasome, a multiproteic complex that mediates the proteolytic cleavage of proinflammatory IL-1β and IL-18. Finally, these modifications are exacerbated by inflammaging, an age-related condition characterized by a persistent inflammation, that carries high susceptibility to comorbidities and death and that can overlap with other inflammatory pathologies or favour their onset, as in the case of CVD (Fig. 1).

Physical activity exerts different effects in the cardiovascular system, including the increase of cardiac output and the decrease of peripheral vascular resistance. In fact, physical activity can provoke a unidirectional shear force in vessels, determining an increase of NO production by endothelial cells. NO-dependent vasodilation favours tissue perfusion and antiatherogenic effects highlighting the beneficial effects of physical activity on a cardiovascular system by improving the endothelium function and, as a consequence, the reduction of inflammation.

**Effects of physical activity on obesity and weight loss**

Over recent decades, obesity has greatly increased in all countries. In the USA, it has been projected that if obesity trends from 2005 to 2020 continue, obesity will increasingly offset the positive effects of declining smoking rates.

### Table 1  Benefits of physical activity on cardiovascular risk factors

| Benefit                                    |
|--------------------------------------------|
| Reduced cardiovascular mortality            |
| Reduced incidence of cardiovascular disease |
| Reduced blood pressure                     |
| Combined with diet-induced weight loss      |
| Improved lipid profile                     |
| Improved immune activation                 |

**Reduced incidence of type 2 diabetes**

**Improved lipid profile**

**Modulated the serum uric acid—hypertension relationship**

© 2019 Italian Federation of Cardiology - I.F.C. All rights reserved.
Obesity is a major risk factor for many CVDs such as coronary heart disease (CHD), heat failure, stroke, ventricular dysfunction and cardiac arrhythmias. The American Heart Association’s scientific statement on obesity and weight loss recommends weight loss in overweight and obese patients to reduce the severity of cardiovascular risk factors. Weight loss in these patients has been associated with improvements in many cardiometabolic risk factors such as prevalence of the metabolic syndrome, insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension, pulmonary disease, CVD and inflammation. Changes in weight are influenced by the amount of energy expended versus that consumed. Therefore, if the energy expenditure remains low, but dietary consumption levels are in excess, weight gain will occur. Several researchers have argued that declines in physical activity both in occupational and leisure time may play an important role in the increase in obesity rates over the last 30+ years. Furthermore, many epidemiological studies suggest that physical activity has an important role in weight gain. An important question is if there is a difference between weight losses, achieved through dietary means, or through ET in terms of cardiovascular risk factors. Ross et al. randomized a group of obese men (n = 52) to diet-induced weight loss, exercise-induced weight loss, exercise without weight loss and a control group for 3 months. The diet-induced and exercise-induced weight loss groups lost approximately 7kg of weight (8% weight reduction), and had significant reductions in total fat mass, visceral fat and increased glucose disposal. However, the ET-induced weight loss group had a greater reduction in total fat mass compared with the diet-induced weight loss group. Importantly, the exercise-induced weight loss improved cardiorespiratory parameters whereas the dietary group did not. In the group who performed ET without weight loss, the participants still experienced reductions in visceral fat and improved cardiorespiratory parameters.

Recent epidemiological evidence has emerged showing greater survival in adults with CVDs with higher obesity levels compared with lower levels, which has been coined ‘the obesity paradox’. Systematic reviews of patients with CAD or undergoing percutaneous coronary intervention supported the ‘obesity paradox’ whereby obesity appears protective. Cardiorespiratory fitness might influence relationships between adiposity and clinical prognosis in the obesity paradox. Normal weight unfit individuals have a higher risk of mortality than fit individuals, regardless of their BMI.

Furthermore, the results of the European Prospective Investigation into Cancer and Nutrition (EPIC) study suggest that the influence of physical inactivity on mortality appears to be greater than that of high BMI.
risk has a continuous positive relationship with BMI and other measures of body fat. Because all-cause mortality appears to increase at BMI levels, European Society of Cardiology guidelines recommend such low BMI levels as treatment goals. Although diet, exercise and behaviour modifications are the mainstay therapies for overweight and obesity, however they are often unsuccessful for long-term treatment.

Results from the EPIC study suggested that the most pronounced risk reductions by increasing levels of physical activity were observed in those categorized as normal weight and abdominally lean. However, across all strata for both general and abdominal adiposity, a markedly reduced hazard was observed between those categorized as inactive or as moderately inactive. Similarly, data from the United States suggest that physical activity reduces but does not eliminate the increased risk of adiposity on all-cause mortality when cross-classifying activity and BMI groups.

In an Asian population a protocol of exercising for 15 min/day (defined as the low-volume exercise group) is associated with a 14% reduction in risk of all-cause mortality compared with inactivity. EPIC study extend these observations to European men and women and suggest that, within each strata for BMI and WC, the hazard of all-cause mortality was substantially reduced when the inactive group was compared with the moderately inactive group. Thus, emerging evidence is accumulating indicating that substantial health benefits may be achieved by fairly small increases in physical activity.

Effects of physical activity on diabetes

T2D estimates have reached pandemic proportions – 327 million in subjects aged 20–64 years worldwide. The presence of diabetes mellitus is associated with a mortality rate of ~1.5%/year which is doubled compared with age-matched controls, with CVD being the primary complication and the leading cause of death in these patients. Lifestyle modification, including physical activity, is the core therapy in all stages of diabetes mellitus.

Indeed, physical activity induces an improvement in insulin sensitivity and in glucose control independently of weight loss, which may further contribute to ameliorate both diabetes-associated defects. A central role in exercise-mediated metabolic changes and in increased contraction-stimulated glucose uptake (via glucose transporter GLUT4 in the sarcolemma and T tubules) is played by adenosine monophosphate (AMP)-activated protein kinase (AMPK), a protein that acts as the energy gauge in the body sensing AMP levels. AMPK-mediated effects have been well described; briefly AMPK activation increases free fatty acid (FFA) oxidation in the liver and muscle, inhibits cholesterol synthesis in the liver and decreases gluconeogenesis and promotes muscle glucose uptake. Another key mechanism to elucidate beneficial effects of physical activity is due to the induced release in myokines from the skeletal muscle, which mediates the crosstalk with adipose tissue, liver, pancreas, bone and brain. Specifically, myokines such as irisin, IL-6, counteract the secretion of proinflammatory adipokines (i.e. resistin, TNF-α, MCP-1) protecting against chronic systemic low-grade inflammation. In addition, irisin regulates liver glycogenesis and gluconeogenesis, and several myokines regulate lipolysis and FFA oxidation in adipocytes (IL-6, IL-15, irisin, myostatin). More recently, it has been shown that physical activity is associated with a reduced risk of having significant CAC in individuals with metabolic syndrome.

In conclusion, while still very much underutilized, fitness should be taken into consideration in everyday clinical risk prediction in addition to the traditional risk factors of the metabolic syndrome and diabetes mellitus.

Interrupting prolonged sitting with 3-min bouts or with light-intensity walking or simple resistance activities (half-squats, calf raises, gluteal contractions and knee raises) every 30 min attenuates acute postprandial glucose, insulin, C-peptide and triglyceride responses in T2D.

These results have been acknowledged in the American Diabetes Association 2018 guidelines which recommend that individuals with diabetes should reduce their sedentary time by breaking up prolonged bouts of sitting with light activity for a few minutes at least every 30 min. The benefits of adherence to physical activity have recently proven to extend beyond surrogate markers of diabetes mellitus late complications (i.e. glucose or A1C) by reducing hard endpoints such as mortality.

Greater adherence to an overall healthy lifestyle defined as eating a high-quality diet, nonsmoking, engaging in moderate to vigorous intensity physical activity, and drinking alcohol in moderation is associated with a substantially lower risk of CVD incidence (~52%) and mortality (~68%) among adults with T2D. Similarly, sedentary time has been shown to increase the risk of all-cause mortality [HR, 1.240 (95% confidence interval [CI], 1.090–1.410)], CVD mortality [HR, 1.179 (CI, 1.106–1.257)] and CVD incidence [HR, 1.143 (CI, 1.002–1.729)].

A few other aspects need consideration. Although there is a robust effect of exercise on insulin sensitivity, a high variability exists in terms of interindividual glycaemic response following physical activity. Pancreatic β-cell function is a stronger predictor of changes in glycaemic control after an aerobic exercise intervention than insulin sensitivity. In a ‘real world’ setting this heterogeneity may simply depend on exercise dose, type, meal timing, drug timing, but also on exercise adherence or exposure to a hyperglycaemic milieu. However, it cannot be
excluded that genetic/epigenetic modifications may account for a reduced/lack of glycaemic response to physical activity.\(^{43}\) Despite these limitations and the possible barriers due to an increased risk of hypoglycaemia occurrence, physical activity in diabetes mellitus should always be encouraged as a key aspect to diabetes mellitus therapy, as also recognized by all International Guidelines.\(^{37}\)

Pedometer data were obtained on 7118 participants and 35.0\% developed diabetes. In an unadjusted analysis each 2000-step increment in the average number of daily steps, up to 10,000, was associated with a 5.5\% lower risk of progression to diabetes (HR 0.95, 95\% CI 0.92–0.97), with more than 6\% relative risk reduction after adjustment.\(^{46}\)

There is some evidence from RCTs that exercise performed 30 min after meal consumption may convey greater improvements in glycaemic control for individuals with T2DM. However, there are only two studies that have directly assessed the role of exercise timing on glycaemic management and adopted methodologies are heterogeneous.\(^{47}\)

Compared with either supervised aerobic or supervised resistance exercise alone, combined exercise showed more pronounced improvement in HbA1c levels; however, there was a less marked improvement in some cardiovascular risk factors. In terms of weight loss, there were no significant differences among the combined, supervised aerobic and supervised resistance exercises.\(^{48}\)

**Effects of physical activity on lipids**

Dyslipidaemia represent one of the strongest independent risk factors for CVD. Among lipoprotein disorders the most strongly related to CVD risk is the plasma level of LDL-C. Other quantitative lipid risk factors are high level of total cholesterol, non-HDL-C, triglycerides (especially if postprandial), apolipoprotein B and Lipo-protein (a). Qualitative risk factors are oxidized LDLs and small dense LDLs. Conversely, plasma HDL-C levels are in some way protective against CVDs.\(^{49}\)

Although the mechanism of exercise-induced lipid changes is unclear, exercise itself may affect lipid metabolism in several ways. In particular, physical exercise could increase endothelial lipoprotein-lipase activity, thus increasing chylomicrons and VLDL triglycerides hydrolysis in granules. Aerobic exercise may also increase the expression of ATP-binding cassette transporter A-1 (ABCA1) thus improving reverse cholesterol transport and HDL-C formation and increase the expression of the Liver X receptor, also improving the ABCA1 expression. Finally, exercise could also reduce the serum level of proprotein convertase subtilisin/kexin type nine thus promoting the removal of LDL-C from plasma by the liver.\(^{50}\) (Fig. 1 Supplemental material, http://links.lww.com/JCM/A192).

The main international guidelines suggest fighting against sedentary behaviour and increasing physical activity to improve the lipid pattern.\(^{51}\) How is it supported by the scientific literature? Physical activity per se does not seem to significantly improve lipid profiles in children, except for a mild irrelevant lowering effect on triglycerides.\(^{52}\)

On the other hand, concurrent aerobic and resistance exercise training led to a significant reduction of LDL-C level (MD = 10.20 mg/dl), even higher in long-term programmes (>24 weeks).\(^{53}\) Walking per se could not have any effect on lipid parameters. However, a mild improvement of LDL-C levels could be observed with longer persistence, and that of triglycerides with longer sessions.\(^{54}\)

A recent large meta-analysis of randomized clinical trials testing the metabolic effect of structured physical exercise (not simply physical activity) showed that exercise training significantly lowered the levels of triglycerides (\(P = 0.02\)) and increased the levels of HDL-C (\(P < 0.001\)) and apolipoprotein A1 (\(P < 0.001\)). The WMDs were 10.63 mg/dl (95\% CI 5.31 mg/dl (95\% CI 1.16–3.87; \(I^2 = 71.8\%\); \(P < 0.001\) for heterogeneity) for triglycerides, 2.32 mg/dl (95\% CI 1.16–3.87; \(I^2 = 87.5\%\); \(P < 0.001\) for heterogeneity) for HDL-C, and 0.03 g/l (95\% CI 0.02–0.04; \(I^2 = 0.0\%\); \(P = 0.81\) for heterogeneity) for apolipoprotein A1. No changes were observed with respect to TC, LDL-C, VLDL-Cholesterol, apolipoprotein B and FFAs. From a clinical point of view, probably the only interesting result is the one related to HDL-C, hardly modifiable by other treatment approaches.\(^{55}\)

In obese subjects, a more marked decrease in triglycerides should be observed, related to the decrease in body weight.\(^{56}\) In elderly, however, physical exercise seems not to be related to an improvement in lipid profiles.\(^{57}\) Probably in this category of subjects lipid profiles could be mildly but significantly improved by techniques like Tai-chi-chuan (Taijiquan).\(^{58}\)

As regards qualitative parameters, physical activity improves the shape of LDLs, increasing the number of large buoyant less atherogenic molecules compared with the more atherogenic small dense ones.\(^{59}\) However, the effect of diet on this parameter seems yet to be more important.\(^{60}\) On the other hand, physical exercise, especially if intensive, could increase the oxidative stress of LDLs.\(^{61}\)

Overall, diet is more effective than physical exercise in improving plasma lipid levels, even if physical exercise can mildly improve the diet efficacy, and has definitely a large number of positive effects on global cardiovascular risk.\(^{62}\)

Finally, statins and exercise combination therapy is more effective than statin monotherapy in terms of insulin sensitivity, inflammation and exercise capacity.\(^{63}\)
Effects of physical activity on blood pressure

The benefits of physical activity on hypertension have been extensively reported. Hypertension has a close relationship with endothelial dysfunction and physical activity is one of several therapeutic strategies for lowering BP. It has been shown that exercise itself promotes an improvement of the redox state and more generally we could say that exercise has direct effects on the vascular wall improving endothelial function via a "vascular condition effect." Cornelissen et al. analysing more than 90 randomized controlled trials, reported that endurance, dynamic and isometric resistance training reduce SBP and DBP; indeed more significant reductions were described for SBP after endurance training [3.5 mmHg (4.6–2.3), P < 0.0001], dynamic resistance training [1.8 mmHg (3.7–0.011), P = 0.049], and isometric resistance training [10.9 mmHg (14.5–7.4), P < 0.0001]; similar results were found for DBP.

Cardio50 is a project of active risk identification and cardiovascular prevention implemented in an Italian cohort of healthy people aged 50. After lifestyle intervention, physical activity increased, whereas metabolic syndrome, impaired fasting glucose and risky drinking decreased. After the intervention, an early reduction in BP and some improvements in lifestyle were observed. This project is coherent with modern strategies based on multifactorial actions.

For this reason current guidelines recommended aerobic exercises for lowering BP and is widely reported that BP reduction decrease CHD risk by 5%, stroke by 8% and all-cause mortality by 4%.

Role of physical activity and urate-lowering drugs on blood pressure control

Uric acid is the final product of purine catabolism and is formed from xanthines and hypoxanthines by the action of the xanthine oxidase, an enzyme expressed in the liver. In normal conditions serum levels of uric acid (SUA) are less than 6 mg/dl in women and 7 mg/dl in men, due to a complex homeostatic regulation mainly involving the kidney transport systems. Hyperuricemia might result from either an overproduction and/or a reduced uric acid renal excretion, thus explaining the large number of factors able to affect SUA levels including age, sex, renal function, the rate of cellular turnover and exogenous/dietary factors, such as purine intake, fructose intake and alcohol consumption. Recent epidemiological data have reported an increasing trend in the prevalence and incidence of hyperuricemia in the general population. Meta-analysis and population-based studies showed that hyperuricemia is frequently associated with atherosclerotic CVD, and that hyperuricemia is an independent risk factor for the development of metabolic syndrome and hypertension. Experimental studies on chronic hyperuricemia also have suggested that elevated SUA may have an independent modulatory or causal role in the development of insulin resistance, which is well established to play a fundamental role in the pathogenesis of all the conditions included in the definition of metabolic syndrome (hypertension, dyslipidemia and impaired glucose homeostasis). Hyperuricemia seems to be a determinant of tissue insulin resistance, mainly affecting insulin clearance and its signalling pathways. Other than by insulin resistance, how high SUA could directly cause hypertension is still unclear, but a progressive renal injury and arterial stiffness, via crystal and crystal-independent mechanisms has been proposed. Both mechanisms eventually lead to a pro-oxidative state and inflammation that cause arteriolosclerosis and ath erosclerosis. It has also been demonstrated that elevated SUA levels may trigger the renin–angiotensin system, directly inhibiting the nitroxide synthesis in the juxtaglomerular apparatus, as in an indirect way, stimulating the proliferation of smooth muscle cells of the afferent arteriolar wall with a consequent reduction of renal perfusion.

Once it is assumed that high SUA is an independent risk factor and a possible cofactor for the development of hypertension, the question arises whether hyperuricemia has a role in BP control. This issue is relevant to understanding whether elevated SUA levels may impair the efficacy of BP-lowering therapy, and/or urate-lowering therapy should be associated with antihypertensive drugs in these cases. The possible role of SUA in altering the efficacy of antihypertensive treatment was studied in a cohort of 2191 subjects enrolled in a survey. SUA levels were significantly higher in untreated hypertensive and uncontrolled hypertensive patients when compared with normotensive subjects and controlled hypertensive patients. Worse BP control was associated with SUA levels, but not with age, BMI, or estimated glomerular filtration rate. These findings showed that high SUA levels could be associated with inadequate BP control in subjects treated with antihypertensive drugs, and subjects with both uncontrolled BP and relatively high SUA levels also had significantly increased arterial stiffness, measured by pulse wave velocity, a factor that could impair BP control during treatment. Furthermore, some experimental and clinical studies demonstrated that lowering serum uric acid levels with xanthine oxidase inhibitors significantly improves SBP and DBP and renal function, accumulating strength and support for the role of hyperuricemia in CVD.

Considering the just mentioned close correlation between hyperuricemia and insulin resistance, and the well documented favourable effect of lifestyle measures for the prevention and treatment of cardiovascular risk factors, a recent trial showed a positive effect of regular physical activity on the SUA-hypertension relationship, pointing to the role of plasma renin activity (PRA) as a possible mediator for this association. PRA in the study was significantly lower in physically active participants.
compared with their sedentary counterparts. This effect on RAS activity could prevent one of the mechanisms whereby hyperuricemia induces BP elevation. Another mechanism by which exercise may counteract the negative effects of high SUA on BP is improved insulin sensitivity. The lower BMI and better metabolic profile shown by active participants compared with their sedentary counterparts attest to a greater insulin sensitivity in the former. The beneficial effect of training on BP via its action on sympathetic activity and on other factors such as improvement of endothelial function and reduction of oxidative stress can have played a role in preventing hypertension development in the active participants.55

Conclusion
In conclusion, due to the several positive effects of physical activity on cardiovascular risk factors, active action is required.

The WHO in their recent program document named ‘Global action plan on physical activity 2018–2030: more active people for a healthier world’ suggested two actions.56 The first is ‘Implement and strengthen systems of patient assessment and counselling on increasing physical activity and reducing sedentary behaviour, by appropriately trained health, community and social care providers, as appropriate, in primary and secondary healthcare and social services, as part of universal healthcare’. The second aims to ‘Enhance the provision of, and opportunities for, appropriately tailored programmes and services aimed at increasing physical activity and reducing sedentary behaviour’. The very recent ACC/AHA Guideline on the Primary Prevention of CVD underlines that ‘Physical activity assessment and counselling in the healthcare setting have important complementary roles in promoting increased physical activity’.57

The Italian Society of Cardiology and the Italian Society of Sports Cardiology are working together to improve the prescription of organized physical activity in patients with CVD and/or cardiovascular risk factors and to produce new guidelines with specific information on organized physical activity.

Acknowledgements
Authors’ contribution: A.V.M. and M.N. conceived of the idea at the basis of the article. M.N., G.P., G.P., M.L.G.B., A.D.C., A.F.G.C., F.F., G.S., M.V., N.G., C.B., U.B., M.P., A.V.M. developed the different part of the article. A.V.M. and M.N. coordinated and assembled the article, A.V.M performed the final supervision. All authors contributed to and approved the final article.

Conflicts of interest
There are no conflicts of interest.

References
1 Thompson PD, Buchner D, Punia L, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003; 107:3109–3116.
2 WHO. Global recommendations on physical activity for health. Geneva, Switzerland: World Health Organization; 2010; https://www.who.int/physicalactivity/factsheet_recommendations/en/.
3 McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Adv Nutr 2011; 2:293–294.
4 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation. Eur Heart J 2016; 37:2315–2381.
5 Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? Can J Cardiol 2016; 32:495–504.
6 Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011; 378:1244–1253.
7 La Gerche A, Heidbuchel H. Can intensive exercise harm the heart? You can get too much of a good thing. Circulation 2014; 130:1092–1102.
8 Frostick J. Immunity, atherosclerosis and cardiovascular disease. BMC Med 2013; 11:117.
9 Rajendran P, Rengarajan T, Thangavel J, et al. The vascular endothelium and human diseases. Int J Biol Sci 2013; 9:1057–1069.
10 Gimbrone MA Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016; 118:620–636.
11 Dearfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007; 116:1295–1295.
12 Kitta Y, Obata JE, Nakamura T, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 2009; 53:323–330.
13 Mudau M, Genis A, Lochner A, Stridom H. Endothelial dysfunction: the early predictor of atherosclerosis. Cardiovasc J Afr 2012; 23:222–231.
14 Rubinshtein R, Kuzin JT, Soffer M, et al. Assessment of endothelial function by noninvasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 2010; 31:1142–1148.
15 Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol 2008; 103:398–406.
16 Park KH, Park WJ. Endothelial dysfunction: clinical implications in cardiovascular disease and therapeutic approaches. J Korean Med Sci 2015; 30:1213–1225.
17 Spillmann F, Van Linthout S, Miteva K, et al. LXR agonism improves TNF-alpha-induced endothelial dysfunction in the absence of its cholesterol-modulating effects. Atherosclerosis 2014; 232:1–9.
18 Edwards N, Langford-Smith AWW, Wilkinson FL, Alexander MY. Endothelial progenitor cells: new targets for therapeutics for inflammatory conditions with high cardiovascular risk. Front Med (Lausanne) 2018; 5:200.
19 Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nat Rev Microbiol 2009; 7:99–109.
20 Nasi M, De Biasi S, Gibellini L, et al. Ageing and inflammation in patients with HIV infection. Clin Exp Immunol 2017; 187:44–52.
21 Cossarizza A, Frasca D. Aging and longevity: an immunological perspective. Immunol Lett 2014; 162:279–280.
22 Nasi M, Pinti M, De Biasi S, et al. Aging with HIV infection: a journey to the center of inflammatory, immunosenescence and neuroHIV. Immunol Lett 2014; 162:329–333.
23 Spence AL, Carter HH, Naylor LH, Green DJ. A prospective randomized longitudinal study involving 6 months endurance or resistance exercise. Conduit artery adaptation in humans. J Physiol 2013; 591:1265–1275.
24 Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. Physiol Rev 2015; 95:549–601.
25 Paravincini TM, Touyz RM. Redox signalling in hypertension. Cardiovasc Res 2006; 71:247–258.
26 Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation 2004; 110:2952–2967.
34 Kraus WE, Yates T, Tuomilehto J, et al. Effects of exercise on cardiovascular risk factors: a meta-analysis of randomized controlled trials in adults. J Am Coll Cardiol 2009; 53:1995–1932.
35 Koster A, Harris TB, Moore SC, et al. Sedentary time and its association with physical activity assessed by pedometer count and new-onset diabetes in adults: a systematic review and meta-analysis. BMJ Open 2015; 5:1925–1932.
36 Mattioli AV, Coppi F, Migaldi M, Farinetti A. Physical activity in sedentary adults with type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2010; 153:175–185.
37 Kuhle CL, Steffen MW, Anderson PJ, Murad MH. Effect of exercise on anthropometric measures and serum lipids in older individuals: a systematic review and meta-analysis. BMJ Open 2014; 4:e000583.
38 Azenzi AM, Alshehn HM, Hoover JC, Yabroudi MA, Kachanathu SJ, Liu W. The effect of Tai Chi exercise on lipid profiles: a systematic review and meta-analysis of randomized controlled trials. J Altern Complement Med 2018; 24:220–230.
39 Kotani K, Tsuzaki K, Sakane N, Taniguchi N. The correlation between small dense LDL and reactive oxygen metabolites in a physical activity intervention in hypertensive subjects. J Hum Hypertens 2018; 32:79–87.
40 Pedersen LR, Olsen RH, Anholm C, et al. Weight loss is superior to exercise in improving the atherogenic lipid profile in a sedentary, overweight population with stable coronary artery disease: a randomized trial. Atherosclerosis 2018; 266:211–217.
41 Medlow P, McEneny J, Murphy MH, Trinick T, Duly E, Davison GW. Lipoprotein subclassification oxidation in acute exercise and ageing. Free Radic Res 2016; 50:345–353.
42 Kelley GA, Kelcy KS, Roberts S, Haskell W. Comparison of aerobic exercise, diet or both on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Clin Nutr 2012; 31:156–167.
43 Gu YJ, Liao CX, Liu Q, et al. Efficacy and safety of statins and exercise combination therapy compared to statin monotherapy in patients with dyslipidaemia: a systematic review and meta-analysis. Eur J Prev Cardiol 2017; 24:907–916.
44 Mattioli AV, Palmiero P, Manfrini O, et al. Mediterranean diet impact on cardiovascular diseases: a narrative review. J Cardiovasc Med (Hagerstown) 2017; 18:925–935.
45 Korsager Larsen M, Matchkov VV. Hypertension and physical exercise: the role of oxidative stress. Medicina (Kaunas) 2016;52:19–27.
46 Mattioli AV, Coppi F, Migaldi M, Farnetti A. Physical activity in premenopausal women with asymptomatic peripheral arterial disease. J Cardiovasc Med (Hagerstown) 2018; 19:677–680.
47 Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension 2011; 58:950–958.
48 Bordin P, Picco F, Valent F, Mattioli B, Vidotto L, Bramanti G. Cardiovascular prevention in 50-year-old adults: an Italian intervention study. J Cardiovasc Med (Hagerstown) 2018; 19:422–429.
49 Williams B, Mancia G, Spiering W, et al. 2013 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2013; 34:215–313.
50 Boghi C, Rosei EA, Bardini T, et al. Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015; 33:1729–1741; discussion 41.
51 Katsiki N, Karagiannis A, Athyros VG, Mikhailidis DP. Hyperuricaemia: more than just a cause of gout? J Cardiovasc Med (Hagerstown) 2013; 14:897–402.
52 Trifiro G, Morabito P, Cavagna L, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005–2009: a nationwide population-based study. Ann Rheum Dis 2013; 72:694–700.
53 Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther 2010; 12:223.
54 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing subtropical management: a nationwide population study. Ann Rheum Dis 2013; 72:661–677.
Role of physical activity in individuals with cardiovascular risk factors Nasi et al. 639

75 Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010; 62:170–180.

76 Wang J, Qin T, Chen J, et al. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PLoS One 2014; 9:e114259.

77 Bonghi C, Cicero AFG. Serum uric acid and cardiometabolic disease: another brick in the wall? Hypertension 2017; 69:1011–1013.

78 Fiorentino TV, Sesti F, Succurro E, et al. Higher serum levels of uric acid are associated with a reduced insulin clearance in nondiabetic individuals. Acta Diabetol 2018; 55:835–842.

79 Tomiyama H, Shina K, Vlachopoulos C, et al. Involvement of arterial stiffness and inflammation in hyperuricemia-related development of hypertension. Hypertension 2018; 72:739–745.

80 Cicero AF, Rosticci M, Bove M, et al. Serum uric acid change and modification of blood pressure and fasting plasma glucose in an overall healthy population sample: data from the Brisighella heart study. Ann Med 2017; 49:275–282.

81 Cicero AF, Rosticci M, Fogacci F, et al. High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects. Eur J Intern Med 2017; 37:38–42.

82 Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008; 300:924–932.

83 Qu LH, Jiang H, Chen JH. Effect of uric acid lowering therapy on blood pressure: systematic review and meta-analysis. Ann Med 2017; 49:142–156.

84 Bove M, Cicero AFG, Borghi C. The effect of xanthine oxidase inhibitors on blood pressure and renal function. Curr Hypertens Rep 2017; 19:95.

85 Saladini F, Mos L, Faria C, Garavelli G, Casiglia E, Palatini P. Regular physical activity prevents development of hypertension in young people with hyperuricemia. J Hypertens 2017; 35:994–1001.

86 World Health Organization. Global action plan on physical activity 2018–2030: more active people for a healthier world. Geneva: World Health Organization; 2018; ISBN 978-92-4-151418-7.

87 Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation 2019; (In press); doi/pdf/10.1161/CIR.0000000000000678.