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 factors. 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.

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

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.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.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).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 CVD2–4 (Table 1).
The aim of this review is to analyse the Endothe-

one of the studies where several were conducted. As a consequence, its antithrombotic properties and IL-18. In fact, 

(Fig. 1).

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Benefits of physical activity on cardiovascular risk factors

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<td>Reduced cardiovascular mortality</td>
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<td>Reduced incidence of type 2 diabetes</td>
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<td>Improved lipid profile</td>
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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 main cardiovascular risk factors and to discuss the main mechanisms involved.

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 event 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 damages is the impairment of the endothelium caused by an excess of stimuli or by a failure of an endothelial repair. As a consequence, its antithrombotic properties are affected, promoting typical pathological changes observed in atherosclerotic CVD. The damage to endothelial cells can be caused by an overcoming of the defence mechanisms of the endothelium, including mechanical stretch due to high blood pressure (BP), metabolites such as reactive oxygen species or innate immune activation. Several conditions have been identified as risk factors for endothelial dysfunction: hypertension, hyperlipidaemia, diabetes, cigarette smoke, homocysteinaemia, ageing and low levels of physical activity. Moreover, endothelial dysfunction represents an independent predictor for cardiovascular events, besides the traditional risk factors.

Endothelial cells have a role in several mechanisms by regulating vasodilation, vasoconstriction, haemostasis, growth of vascular smooth muscle cells (VSMC), interaction between leukocytes and inflammation. Endothelium can be damaged by increased vasoconstriction, platelet aggregation and adhesion leading to a prothrombotic state, by an increased smooth muscle proliferation and vascular inflammation. Nitric oxide (NO) is one of the most important endogenous vasodilators produced by endothelial cells having 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 endothelium-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 inflamaging, 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.

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 vasodilatation 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.
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. 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 7 kg 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.33,34

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.35 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.36 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.37 Lifestyle modification, including physical activity, is the core therapy in all stages of diabetes mellitus.37

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.38,39 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).40 More recently, it has been shown that physical activity is associated with a reduced risk of having significant CAC in individuals with metabolic syndrome.41

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.42

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.37

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.42 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)].43

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.44 Pancreatic β-cell function is a stronger predictor of changes in glycaemic control after an aerobic exercise intervention than insulin sensitivity.44 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. 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.

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.

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

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.

**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 Lipoprotein (a). Qualitative risk factors are oxidized LDLs and small dense LDLs. Conversely, plasma HDL-C levels are in some way protective against CVDs.

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 (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. 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.

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). 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.

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 −5.31 mg/dl (95% CI −10.63 to −0.97; F = 71.8%; P < 0.001 for heterogeneity) for triglycerides, 2.32 mg/dl (95% CI 1.16–3.87; F = 87.5%; P < 0.001 for heterogeneity) for HDL-C, and 0.03 g/l (95% CI 0.02–0.04; F = 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.

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

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. However, the effect of diet on this parameter seems yet to be more important. On the other hand, physical exercise, especially if intensive, could increase the oxidative stress of LDLs.

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.

Finally, statins and exercise combination therapy is more effective than statin monotherapy in terms of insulin sensitivity, inflammation and exercise capacity.
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’.

Recent epidemiological data have reported an increasing trend in the prevalence and incidence of hyperuricemia in the general population. 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.

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.

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 athrosclerosis. 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 arteriole 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.
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. 58

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’. 57

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’. 58

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.

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Conflicts of interest

There are no conflicts of interest.

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