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Abstract

Metabolic syndrome and its various features (obesity, hypertension, dyslipidemia, diabetes, and nonalcoholic fatty liver disease) are increasing worldwide and constitute a severe risk for the sustainability of the present universal Italian health care system. Lifestyle interventions should be the first therapeutic strategy to prevent/treat metabolic diseases, far before pharmacologic treatment. The role of diet and weight loss has been fully ascertained, whereas the role of physical activity is frequently overlooked both by physicians and by patients. Physical activity has favorable effects on all components of the metabolic syndrome and on the resulting cardiovascular risk, the cornerstone in the development of cardiometabolic diseases. The quantity and the frequency of physical activity necessary to produce beneficial effects has not been defined as yet, but brisk walking is considered particularly appropriate, as it can be practiced by a large number of individuals, without any additional cost, and has a low rate of injury. The effects of exercise and leisure time physical activity extend from prevention to treatment of the various components of the metabolic syndrome, as well as to mood and quality of life. Any effort should be done to favor adherence to protocols of physical activity in the community.

Keywords (separated by '-') Diet - Exercise - Lifestyle - Metabolic syndrome - Physical activity

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IM - REVIEW

Physical activity for the prevention and treatment of metabolic disorders

Luca Montesi · Simona Moscatiello · Marcella Malavolti · Rebecca Marzocchi · Giulio Marchesini

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Abstract Metabolic syndrome and its various features (obesity, hypertension, dyslipidemia, diabetes, and nonalcoholic fatty liver disease) are increasing worldwide and constitute a severe risk for the sustainability of the present universal Italian health care system. Lifestyle interventions should be the first therapeutic strategy to prevent/treat metabolic diseases, far before pharmacologic treatment. The role of diet and weight loss has been fully ascertained, whereas the role of physical activity is frequently overlooked both by physicians and by patients. Physical activity has favorable effects on all components of the metabolic syndrome and on the resulting cardiovascular risk, the cornerstone in the development of cardiometabolic diseases. The quantity and the frequency of physical activity necessary to produce beneficial effects has not been defined as yet, but brisk walking is considered particularly appropriate, as it can be practiced by a large number of individuals, without any additional cost, and has a low rate of injury. The effects of exercise and leisure time physical activity extend from prevention to treatment of the various components of the metabolic syndrome, as well as to mood and quality of life. Any effort should be done to favor adherence to protocols of physical activity in the community.

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Keywords Diet · Exercise · Lifestyle · Metabolic syndrome · Physical activity

Introduction

The epidemic of metabolic disorders, driven by obesity, constitutes a challenge for health systems worldwide. Several factors are contributing to the increasing prevalence of the various features of the metabolic syndrome (hypertension, dyslipidemia, and type 2 diabetes). Diet and lifestyle have a major role, coupled with genetics. Positive economic developments and better healthcare, favoring population aging, are expected to increase costs to levels no longer sustainable both in Western and in developing countries. For the hundreds of millions worldwide who have the "metabolic syndrome", lifestyle modification is the most appealing approach because of its non-toxicity and high efficacy, compared with medications, and physical activity (PA) is a fundamental component.

It is outside the scope of the present review to discuss the reason(s) and the real existence of the syndrome, i.e., whether a residual risk exists above that conferred by individual features or old and new cardiovascular risk factors [1]. Lifestyle modifications are mandatory for the individual components, and more so when they sum up, not only in the case of overt disease, but also when the individual components are in the range of "pre-disease" (i.e., prediabetes, prehypertension, mild dyslipidemia not requiring drug treatment or low-grade visceral fat accumulation) [2]. This is the reason for the progressive reduction of the diagnostic cut-offs that occurred along the years (Table 1) (see [3, 4].

Table 1 Diagnostic criteria of the metabolic syndrome, as proposed by different International Agencies (see [3, 4])

	WHO (1999)	EGIR (1999)	ATPIII (2001–rev 2005)	AACE (2003)	IDF (2005–rev 2009)
Data required	IR (upper quartile of general population) OR glucose ≥110 mg/dL; OR 2-h glucose ≥140 mg/dL	IR OR fasting insulin, in the upper quartile of general population NO diabetes	None	High risk for IR OR BMI ≥25 kg/m^2	Ethnic-based WC: Caucasian ≥94 cm (men) or ≥80 cm (women); Asian ≥90 cm (men) or ≥80 cm (women)
No. of additional abnormalities	≥2 of the following	≥2 of the following	≥3 of the following	≥2 of the following	≥2 of the following
Glucose		≥110 mg/dL	≥100 mg/dL OR on medications	≥110 mg/dL; 2-h ≥140 mg/dL	≥100 mg/dL OR on medications
HDL cholesterol	<35 mg/dL (men); <40 mg/dL (women)	<40 mg/dL	<40 mg/dL (men), <50 mg/dL (women) OR on medications	<40 mg/dL (men), <50 mg/dL (women)	<40 mg/dL (men), <50 mg/dL (women) OR on medications
Triglycerides	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL OR on medications	≥150 mg/dL	≥150 mg/dL OR on medications
Obesity	Waist to hip ratio: >0.9 (men), >0.85 (women); OR BMI ≥30 kg/m^2	WC ≥94 cm (men), ≥80 cm (women)	WC >102 cm (men), >88 cm (women)		See required parameters
Blood pressure	≥140/90 mmHg	≥140/90 mmHg	≥130/85 mmHg OR on medications	≥130/85 mmHg	≥130/85 mm Hg OR on medications
Other	Microalbuminuria				

WHO world Health Organization, *EGIR* European Group on Insulin Resistance, *ATPIII* Adult Panel Treatment III, *AACE* American Association of Clinical Endocrinologists, *IDF* International Diabetes Federation, *WC* waist circumference, *IR* insulin resistance, *BMI* body mass index

We discuss the evidence supporting a major role for PA both in the prevention and treatment of metabolic disorders, over and above the effects on weight loss. For the individual components of the metabolic syndrome, the data on hard outcomes (mortality and cardiovascular events) will be separated from the effects on surrogate markers (body weight, blood pressure, lipid, and glucose control).

Obesity

Obesity, namely abdominal obesity, is a well-proven risk factor for coronary heart disease (CHD), whereas PA reduces the risk [5]. Although the significance of overweight and class I obesity on overall mortality has very recently been challenged [6], weight loss is mandatory to reduce cardiovascular risk in obese subjects and any intervention on lifestyle includes PA as necessary component. Limiting the importance of PA to weight loss is, however, reductive; PA is a cornerstone for the treatment of non-communicable disease, independently of weight loss. The amount of calories burned by exercise is probably of minor importance compared with the calorie deficit generated by dietary restriction and PA only becomes pivotal for long-term weight loss maintenance [7].

This view is supported by a very recent randomized controlled trial (RCT), comparing the effects of diet, exercise, or the combination of diet and exercise [8]. Exercise significantly improved the functional status, without any effect on body weight; diet significantly reduced body weight, whereas combination treatment more significantly improved physical performance. Similarly, in postmenopausal women, diet was more effective than a physical activity program on weight loss at 1 year (−8.5 vs. −2.4 %), but the combination of diet + physical activity produced additive effects (−10.8 %) [9].

Pre-hypertension/hypertension

Hypertension is an independent risk factor for cardiovascular disease and a relationship exists between blood pressure (BP) levels and CHD [5] in spite of remarkable advances in therapy [10]. Drug-treated hypertensive patients are still at risk for future cardiac events [11] and behavior therapy, including healthy diet and increased PA,

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remains the background approach because of its beneficial effects from the pre-hypertensive stage [12].

In a systematic review of lifestyle interventions in hypertensive patients, Dickinson et al. [13] found robust evidence for the beneficial effects of a healthy diet, aerobic exercise, alcohol and sodium restriction, and fish oil supplements. This evidence supports the prescription of a low-sodium diet, or of a diet with the characteristics of the Dietary Approaches to Stop Hypertension (DASH) program [14]. The DASH diet, based on the computation of servings, was specifically developed to help people prevent or treat hypertension, by reducing the levels of total fat, saturated fat and cholesterol, and increasing potassium, calcium, magnesium, fiber, and proteins. Such dietary changes have been shown to reduce blood pressure, mainly systolic BP by 2–14 mmHg in about one month [14], also depending on the amount of weight loss that may produce an additional 5–20 mmHg reduction in systolic BP. In subjects with prehypertension or stage-1 hypertension of the PREMIER study, 180 min/week of PA or more, alone or in combination with the DASH diet, significantly reduces the estimated CHD risk in an 18-month follow-up [15].

When superimposed upon dietary changes, exercise per se may reduce both systolic and diastolic pressure by another 5–7 mmHg [16], and exert favorable effects on a variety of cardiovascular risk factors, in a dose-dependent fashion, after correction for confounders [17]. Low levels of cardio-respiratory fitness are associated with a high risk of mortality, and improved fitness is associated with a reduced mortality risk. In a 20-year follow-up of North American women, low physical fitness is associated with a 20 % increased risk of cardiovascular death for every metabolic equivalent (MET) decrease in exercise capacity [18]. Exercise training produces a graded dose response in fitness in sedentary, overweight, or obese postmenopausal women at moderately high risk of cardiovascular disease [19]. Also moderate levels of fitness induced by exercise are associated with a lower risk for all cause and cardiovascular disease mortality, both in individuals with elevated BP and in those without a diagnosis of hypertension.

In both normotensive and hypertensive healthy sedentary individuals, any type of exercise (i.e., walking, jogging, running, and cycling) is beneficial, including resistance training. Walking remains the preferred form of exercise as it may be recommended by healthcare professionals to the majority of patients, even the elderly, with few exceptions. A systematic search of the literature identified 27 randomized controlled trials on the effects of walking on blood pressure and nine of them were positive [20]. The beneficial effect on blood pressure control is mainly observed in trials of moderate- to high-intensity walking and of longer duration, suggesting that recommendations should focus on walking intensity and treatment adherence [20]. Regular walking programs and pedometers for monitoring PA may favor adherence to exercise programs in normotensive, overweight adults. Pedometers may also increase the motivation for PA; they were used to monitor walking programs in 26 studies (8 randomized controlled trials and 18 observational studies), where pedometer users significantly increase PA by 26.9 % over baseline. A goal of 10,000 steps/day is necessary to achieve the desired effects, i.e., reduced BP and reduced BMI [21]. In a recent study, walking decreased adjusted mean systolic and diastolic blood pressure by 7–9 % [22].

The PA-induced effects on BP translate into reduced morbidity and mortality in hypertensive patients. When self-reported PA was graded in a prospective, randomized hypertension study (the LIFE study) exercising >30 min twice/weekly is associated with a reduced cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy in a 4.8-year follow-up [23]. Aerobic exercise combined with dietary modification (DASH diet) in sedentary overweight and obese patients with high BP (above the cut-offs for the metabolic syndrome) also improved neurocognitive functioning [24]. In a short-term trial, aerobic exercise consisting of moderate-to-vigorous intensity exercise according to current guidelines [25] also reduced both radial and femoral pulse wave velocity [26]. Similarly, exercise training and weight reduction (cycle ergometer training twice a day, 5 days a week, and hypocaloric diet) in patients with drug-treated hypertension reduced BP and cardiovascular risks, and improved abnormal left ventricular relaxation [27].

It is definitely time to move from interventions limited to specialist centers to community-based PA implementation for the control of hypertension, with the support of new technologies to stimulate adherence. In subjects aged 60 and over with mild to moderate hypertension, a 6-month community-based walking intervention based on self-efficacy theory, including both face-to-face and telephone support designed to assist participants to increase their walking, decreases systolic blood pressure by 15 mmHg, with no difference in diastolic pressure [28].

Dyslipidemia

Less than optimal lipid and lipoprotein levels, particularly elevated levels of low-density lipoprotein (LDL) cholesterol, increase the risk for morbidity and mortality from CHD throughout the range of lipid and lipoprotein values [29]. Lifestyle intervention should be the first therapeutic strategy for "cardio-metabolic" patients and international agencies recognize regular PA as an essential component of a lifestyle modification program [29].

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High levels of PA and cardio-respiratory fitness are associated with reduced risks of morbidity, mortality, and improvement of their prognostic risk factors [30, 31], but the optimal intensity or amount of exercise necessary for risk reduction is unknown. As for hypertension, brisk walking is the most commonly suggested type of PA. Current guidelines suggest moderate intensity activity for ≥30 min/session at least 5 days/week, but there is no definite evidence on the amount of exercise conferring specific health benefits.

In sedentary overweight men and women, increasing the amount and intensity of exercise significantly reduces small, dense LDL particles, increases LDL particle size and high-density lipoprotein (HDL) cholesterol, and reduced triglyceride levels. Improvements are neither related to the intensity of exercise or improved fitness, nor to the minimal weight change, but only to the amount of activity [32]. A meta-analysis of 25 studies including over 1,000 subjects confirms that regular PA reduces the ratio of total to HDL-cholesterol (decreasing by about 6 %), as well as the plasma levels of HDL-cholesterol and triglycerides [33], although the latter changes are not statistically significant.

The independent effects of exercise intensity and amount have not been conclusively established yet. A systematic review of 28 randomized studies of moderate-to-hard intensity PA for 12 weeks or longer shows a large variability in lipid response, with a significant increase in HDL-cholesterol levels in approximately 40 % of trials [34]. In a more recent trial on sedentary treatment-naïve adults (almost two-thirds women), comparing four exercise regimens (moderate vs. hard intensity and low vs. high frequency in a 2 × 2 model), the hard-intensity high-frequency exercise regimen is the only intervention that produces a significant improvement in HDL cholesterol compared with physician advice alone, suggesting that both intensity and frequency are important [35]. In a different study [32], the high-intensity high-volume exercise, not the high-intensity low-volume or the low-intensity low-volume exercise over 8 months significantly increases HDL-cholesterol level. Thus, changes in HDL may depend on the intensity, frequency, and volume of exercise, and on the individual's baseline level [34]. In a more recent trial [36], patients assigned to high-amount exercise show improvements in HDL size, which are sustained for up to 2 weeks after exercise withdrawal. This benefit may be clinically important, as HDL-cholesterol particles have anti-inflammatory, antioxidative, anti-platelet, anticoagulant, and pro-fibrinolytic activities, in addition to their role in reverse cholesterol transport. Moreover, moderate-intensity, but not vigorous-intensity, exercise results in a sustained reduction in very low-density lipoprotein (VLDL)-triglycerides over 15 days of detraining.

Historically, LDL cholesterol has long been considered a primary risk factor for cardiovascular disease, but the multinational INTERHEART study shows that the apolipoprotein (apo)B/apoA-I ratio is the most important modifiable predictor of myocardial infarction [5]. ApoB is a direct measure of the number of atherogenic particles as there is a single apoB molecule present on the surface of all LDL, intermediate density lipoprotein, and VLDL particles. ApoA-I is the major protein on HDL particles and thus provides an indication of the number of anti-atherogenic particles [37]. Cross-sectional studies associate lower apoB levels with high levels of PA [38] and longitudinal studies show that regular exercise reduces apoB by up to 20 % [39]. In physically inactive, middle-aged men who are overweight, PA reduces apoB levels as well as the apoB/apoA-I ratio without effect on LDL cholesterol [39]. Finally, in obese and insulin-resistant patients, moderate PA is associated with decreased apoB/apoA-I ratio and increased apoA-I, whereas vigorous PA is required to observe a reduction in apoB [40], after adjustment for smoking, systolic blood pressure, and waist circumference.

In summary, PA has a remarkable effect on the lipid profile, one of the most relevant modifiable risk factors for CHD morbidity and mortality. This conclusion has, however, been challenged by a very recent paper showing that objectively measured sedentary time is the most important lifestyle factor associated with a poor metabolic profile (altered triglycerides, HDL-cholesterol, glucose) after adjustment for BMI and moderate-to-vigorous physical activity [41]. These data further indicate the importance of implementing leisure-time PA in the community to reduce the burden of metabolic diseases, as sedentary behavior, per se, is associated with increased cardiovascular mortality [42].

Prediabetes/diabetes

There is strong evidence that the occurrence of both prediabetes and type 2 diabetes (T2DM) is strictly associated with low cardio-respiratory fitness. In a seminal report of the Nurses' Health Study, Hu et al. [43] report that the relative risk of developing T2DM is reduced across quintiles of time spent per week on each of eight common PAs, including walking, during an 8-year follow-up (over half million person-years). Faster than usual walking pace is independently associated with decreased risk, but equivalent energy expenditures similarly promoted risk reduction. Several clinical trials confirm that PA is an effective tool for the prevention and management of altered glucose metabolism.

Prevention studies (Table 2)

Four large-scale, multi-centre, randomized clinical trials are the corner stones in the evidence of the benefits of PA

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Table 2 Most important RCT on physical activity (with/without dietary counseling) in the prevention of type 2 diabetes

Study (Ref.)	No. Pz.	Arms	Objectives	Study duration and follow-up	Results
Finnish Diabetes Prevention Study [45, 50]	522	Intensive lifestyle Control	Weight loss ≥5 % Total intake of fat <30 % Saturated fat <10 % Intake of fiber ≥15 % for 1,000 kcal ≥30 min/day of moderate-intense PA	3.2 years (F-UP, 3 years)	Progression to T2DM: −58 % during the intervention period, −36 % during F-UP
US Diabetes Prevention Program [44, 48]	3,234	Intensive lifestyle intervention (ILI) Metformin (MET) Placebo (PL)	Weight loss ≥7 % ≥150 min/week of moderate PA	3.2 years (F-UP 10 years)	Progression to T2DM: −58 % (ILI), −31 % (MET) during the study No differences in T2DM incidence in F-UP (most cases received ILI in MET and PL groups) Overall 10-years effect: −34 % (ILI), −18 % (MET)
Da Qing Chinese study [47, 49]	577	Only diet Only PA Diet + PA Control	Weight loss of 0.5–1.0 kg/month, Increase in PA >1–2 U/day (1 U = 30 min of mild PA, 20 min if moderate, 10 min if intense, 5 min if very intense) 25–30 kcal/kg (55–65 % CHO, 10–15 % protein; 25–30 % fat) Increase in vegetables Reduced alcohol and CHO intake	6 years	Progression to T2DM: −31 % (diet), −46 % (PA), −42 % (diet + PA) during the study period Cumulative incidence of T2DM during the 20-year F-UP: 80 % combined treatment, 93 % placebo group
Indian Diabetes Prevention Program [46]	531	Lifestyle (LSM) Metformin (MET) LSM + MET Control	Reduced total calorie intake Reduced CHO and fat intake No sugar Increased fiber intake Moderate PA >30 min/day	30 months	Progression to T2DM: −28,5 % (LSM), −26,4 % (MET), −28,2 % (LSM + MET)
DPP in Primary Care [52]	241	Coach-led group Self-directed intervention Usual care	Lifestyle change coaching and support remotely-through secure email within an electronic health record system and the American Heart Association Heart360	15 months	Weight loss >7 %: 37.0 % (coach-led group), 35.9 % (self-directed group), 14.4 % (usual care)
Korean National Health Insurance Corporation [52]	7,233	Exercise group Control	Warm-up, (10–15 min), aerobic (25–30 min; e.g., treadmill or cycling), resistance (10–15 min; e.g., bench press, arm curl, etc.) and cool-down (10–15 min; relaxation and stretching) 3 times/week for 6 months	2 years	Progression to T2DM: −23 % Weight: −1.5 kg Waist circumference: −3 cm

CHO carbohydrates, *DPP* Diabetes Prevention Program, *F-UP* follow-up, *ILI* intensive lifestyle intervention, *LSM* lifestyle modifications, *MET* metformin, *PL* placebo, *RCT* randomized controlled studies, *PA* physical activity, *T2DM* type 2 diabetes mellitus

in a prediabetic population. The US Diabetes Prevention Program (DPP) reports a 58 % reduction in the incidence of T2DM after an average of 2.8 years of lifestyle intervention aimed at 150 min/week of moderate-intensity PA and dietary restriction to induce a 7 % weight loss [44]. A perfectly identical risk reduction of 58 % is associated with lifestyle changes in the Finnish Diabetes Prevention Study (DPS) [45]. In Asian Indians with impaired glucose tolerance (IGT), lifestyle modifications, including 210 min/week of brisk walking and dietary modifications, reduces the risk of incident diabetes by 28 % [46], whereas the Chinese Da Qing study demonstrates a risk reduction of incident diabetes of 31, 46, and 42 %, respectively, in subjects with IGT in a follow-up of 6 years of three intervention groups (diet only, exercise only, and diet plus exercise), independent of obesity [47]. Long-term follow-ups of these studies confirm that systematic interventions to improve lifestyle habits maintain the beneficial effects up

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to 20 years [48–51]. Of note, the methodology of the Diabetes Prevention Program also is effective in a primary care setting, coupled with technology to increase physician–patient communication (E-LITE study) [52].

All these studies were carried out adding nutritional modification/counseling to PA. A recent prospective cohort study observed the effects of a 6-month program based on exercise only (300 min/week of moderate-intensity exercise) in a large group of Korean subjects with normal or impaired fasting glucose [53]. During a 2-year follow-up, regular exercise is associated with a 23 % risk reduction of incident T2DM, particularly in subjects with overweight/obesity, where reduced waist circumference and BMI are associated with reduced fasting glucose levels. These results are in keeping with the hypothesis that regular exercise might prevent diabetes via reduced obesity or body fat redistribution, a conclusion not fully supported by obesity studies [8]. The EPIC-InterAct case-cohort study specifically addressed the relative role of PA and weight loss on incident T2DM in men and women [54]. Higher levels of PA are associated with a significant risk reduction across BMI categories, in the presence and absence of visceral adiposity, confirming that PA prevents T2DM regardless of adiposity and weight loss.

Based on the above evidence, health agencies recommend at least 150 min/week of moderate to vigorous aerobic-based exercise to prevent T2DM, but we need to move from a prescriptive model to a comprehensive battle against sedentary lifestyle [41, 55].

Intervention studies (Table 3)

The beneficial effects of PA and improved cardiorespiratory fitness on metabolic control in T2DM finds support in the Look AHEAD (Action for Health in Diabetes) study. This multicenter randomized controlled trial of over 5,000 overweight or obese people with T2DM transposed the general framework of the Diabetes Prevention Program in the field of intervention. An intensive lifestyle intervention (ILI), aimed at achieving and maintaining a weight loss of

Table 3 Randomized controlled studies of physical activity intervention in individuals with T2DM

Study (Ref.)	No. Paz.	Arms	Objectives	Follow-up	Results
Di Loreto et al. [59, 60]	182	Behavioral approach Control	Energy expenditure >10 MET/h/week from baseline PA levels Diet (55 % CHO, 30 % fat, 15 % protein) −300 kcal/die if BMI >25 kg/m^2	2 years	Targets achieved: 69 % intervention; 18 % control; Significant improvements in BMI, blood pressure, HbA1c, T2DM costs
Look AHEAD Study [56–58]	5,145	Intensive lifestyle intervention (ILI) Diabetes support and education (DSE)	Weight loss ≥7 % at 1 year and long-term maintenance 1,200–1,800 kcal depending on the initial weight Total fat <30 % Saturated fat <10 % Protein ≥15 % 175 min/week of moderate PA	4 years	Results at 4 years: weight loss: −6.15 % (ILI) vs. −0.88 (DSE) Fitness: +12.7 vs. +1.9 % HbA1c: −0.36 % (ILI) vs. −0.09 % (DSE) Improvement in BP and dyslipidemia Remission of T2DM: 9.2, 6.4, and 3.5 % at 2, 3, 4 years in ILI vs. 1.7, 1.3, 0.5 in DSE
Italian Diabetes Exercise Study [61–63]	606	Exercise (EXE) Control	150 min/week of PA (aerobic and resistance training) in 2 sessions Diet (55 % CHO, 30 % fat, 15 % protein) −500 kcal/die if BMI >25 kg/m^2	1 year	Results at 1 year: HbA1c: −0.49 % (EXE) vs. −0.10 % (control) Improvement in blood pressure and dyslipidemia (EXE) Increase in VO_2max (EXE), independently of WL
Bacchi et al. [64]	40	Aerobic group (AER) Resistance group (RES)	3 times/week for 60 min	4 months	Short-term results: HbA1c: −0.40 % (AER) vs. −0.35 % (RES) VO_{2peak}: 4 ml^{-1} kg min^{-1} (AER) vs. 2.1 (RES)

AER aerobic activity group, *BMI* body mass index, *BP* blood pressure, *CHO* carbohydrates, *DSE* diabetes support and education, *EXE* exercise, *ILI* intensive lifestyle intervention, *MET* metabolic equivalent, *PA* physical activity, *RES* resistance activity group, *T2DM* type 2 diabetes mellitus, *VO_2* oxygen consumption, *WL* weight loss

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7 % through diet and increased PA (175 min/week) was compared with standard education. The primary endpoint of the study was a composite outcome consisting of incident cardiovascular events, to be tested after a programmed follow-up of 13.5 years. The results at 12- and 48-month follow-up in over four thousand individuals are encouraging: subjects who completed the 1-year trial improve their cardiorespiratory fitness (assessed using a sub-maximal graded exercise test) [56], after adjustment for baseline fitness (20.9 % in ILI vs. 5.7 %; $P < 0.001$) and also a modest weight loss (5–10 %) is associated with improved cardiovascular risk factors. These benefits are partly maintained at 4 years [57]. However, a very recent re-analysis of ongoing data showed that the expected differences in cardiovascular outcome could no longer be attained and the study was terminated because of futility on October 2012. Termination was unexpected, also considering that the study had shown remission of diabetes in up to 10 % of treated cases in the ILI group, compared with 1–2 % in the standard care group [58].

In the Italian setting, Di Loreto et al. [59] show that 2 years of regular aerobic exercise in a diabetic population reduces all aspects of the metabolic syndrome. Any graded 10 MET-h/week of PA (corresponding to a 30-min walk/day), after a course of structured PA, reduces BMI and improves HbA1c [60]. Of note, in the intervention group, drug treatment, and the overall direct cost of diabetes are reduced in parallel with decreased estimated 10-year coronary risk [59].

Also the type and mode of PA can make a difference. In the Italian Diabetes and Exercise Study (IDES) an ILI based on planned and supervised, mixed exercise (aerobic and resistance training) improved HbA1c and reduced the cardiovascular risk [61]. The intensive program of 150 min/week in two divided sessions of aerobic and resistance exercise supervised by a trainer, associated with dedicated counseling produced significant benefits in a 12-month follow-up; patients started exercising also outside gym sessions [61] and their quality of life improved systematically in relation to the attained PA volume. In a pre-specified analysis of the IDES cohort, the benefits of PA/exercise are once again independent of weight loss [62], and in low-fitness, sedentary individuals with T2DM, increasing exercise intensity was not harmful, but did not provide additional benefits on cardiovascular risk factors [63]. The benefits of resistance exercise were confirmed in the RAED2 study [64] and in insulin-treated T2DM [65].

Nonalcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease is characterized by liver triglyceride accumulation (steatosis) in subjects with no history of excessive alcohol intake. NAFLD encompasses a large histological spectrum, from simple steatosis, to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, potentially progressing to hepatocellular carcinoma [66]. It is the most common cause of chronically elevated liver enzymes and chronic liver disease, affecting 20–35 % of the general adult population in the Western countries. Although the prevalence is higher in the age group between 40 and 70 years, NAFLD is present in almost all age ranges, including the pediatric population, with a prevalence of ~10 % in children and adolescents, which is expected to rise sharply as an effect of the growing epidemic of obesity in childhood and adolescence [67].

NAFLD is regarded as the hepatic expression of the metabolic syndrome, considering its close association with all its components [66, 68], similar pathophysiological mechanisms based on insulin resistance [69], and a similar cardiovascular risk [70]. Liver fat is indeed associated with a diffuse cardiovascular involvement (increased intima-media thickness and the presence of carotid plaques), independently of the presence of T2DM, and by endothelial dysfunction [71]; the outcome is strictly dependent on cardiovascular events [72], adding to liver-associated morbidity and mortality, as well as to cancer mortality [73].

In the absence of specific pharmacological treatments and considering the strong association between NAFLD, metabolic syndrome, insulin resistance and other metabolic abnormalities [74], prevention and treatment are mainly directed at improving insulin sensitivity and at correcting cardiometabolic risk factors [66, 75]. These objectives are achieved through a first-level intervention that consists in lifestyle change, calorie restriction, and increased PA. PA is expected to achieve these objectives, independently of weight loss [76, 77]. The beneficial effects of exercise on liver steatosis and biochemical tests became clinically significant after a very short-term program of aerobic exercise (treadmill walking for 60 min/day on 7 consecutive days at 85 % of maximal heart rate): the biochemical profile is improved, the markers of hepatocyte apoptosis are reduced, and the whole body fat oxidation is increased [78]. Exercise programs of longer duration (4 weeks to 6 months) generate additional benefits and reduce the intrahepatic triglyceride content [77, 79], serum aminotransferase levels [80], insulin resistance [81, 82], and even improve the histological pattern (NAS score at liver biopsy) [83] in relation to changes in body weight or body composition [83]. These benefits are also demonstrated in adolescents [84]. However, no study has so far demonstrated a significant effect of behavior treatment (including PA implementation) on hard outcomes, including mortality, cardiovascular events, or progression to cirrhosis.

Individual reports of exercise interventions often have low sample sizes and insufficient power to detect clinically

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meaningful hepatic benefits and most of them include contemporary dietary counseling, which does not allow an independent evaluation of PA. In general, there are no accepted criteria for the optimal intensity, duration, or total volume of exercise to obtain these beneficial effects and the meta-analysis can only be used to substantiate the 'global benefit' of exercise therapy on liver fat. In a systematic review with meta-analysis on the efficacy of exercise interventions (from 2- to 24-week duration, exercise on 2–6 days/week, intensity 45–85 % of VO_2 peak), Keating et al. [85] found six studies directly comparing exercise vs. a non-exercise control arm on liver fat and serum ALT in adults. In 6/12 selected studies, the results favor exercise. By pooling the data (156 adults, mostly overweight or obese), there is clear evidence for a systematic benefit of exercise on liver fat, with minimal or no weight loss. There is no effect on serum ALT levels, which are normal at baseline in several reports. In addition, PA improves cardiovascular risk factors including hypertension, T2DM, dyslipidemia, visceral adiposity and reduces the absolute cardiovascular risk [85]. In a cross-sectional analysis of subjects enrolled in the US NASH Clinical Research Network, only vigorous exercise, not moderate exercise, nor total duration or volume of PA, are associated with decreased odds of having NASH or advanced fibrosis [86]. The biological basis for this difference is unknown.

In conclusion, the intensity of PA/exercise may be an important dimension to consider when counseling patients and planning interventions. Intervention studies with objective measures of PA are required to confirm the differential effects of vigorous compared with moderate PA on NAFLD severity [87]. At present, experts recommend 30 min of moderate intensity PA on most days of the week [81], or vigorous-intensity PA ≥3 times per week for ≥20 min each time [87]. Implementation of PA remains the more demanding challenge because there is evidence that counseling about the benefits of exercise or exercise prescription does not translate into positive outcomes [81].

A lot of psychological and physical barriers reduce adherence to PA in NAFLD, and motivation may be low in most cases [88]. NAFLD subjects are characterized by a sedentary lifestyle [89, 90], also due to physical factors objectively limiting exercise, such as fatigue [91], reduced cardiorespiratory fitness [90, 92], osteoarthritis linked with obesity and associated cardiovascular disease. From physicians' perspectives, the barriers to promote exercise as therapy for NAFLD are the scarce confidence with educational programs, lack of training in communication and group management, the awareness of future scarce adherence of patients, and their high dropout rate from lifestyle interventions [93]; from patients' perspectives, barriers include climate factors, perceived effort of exercise and lack of time, as well as lack of self-efficacy [94]. A structured program of cognitive behavioral therapy may favor lifestyle changes, increasing the probability to reduce body weight, to normalize liver enzymes, and to reduce the number of features of the metabolic syndrome [95].

In conclusion, as with other chronic diseases related to unhealthy behaviors, we need a global strategy to reduce the burden of NAFLD [96]. Interventions should include strategies to promote regular contacts with a health care professional, self-monitoring, and individual goal setting, considering the large differences present in the community. This is the way to disseminate PA in a sedentary population [81].

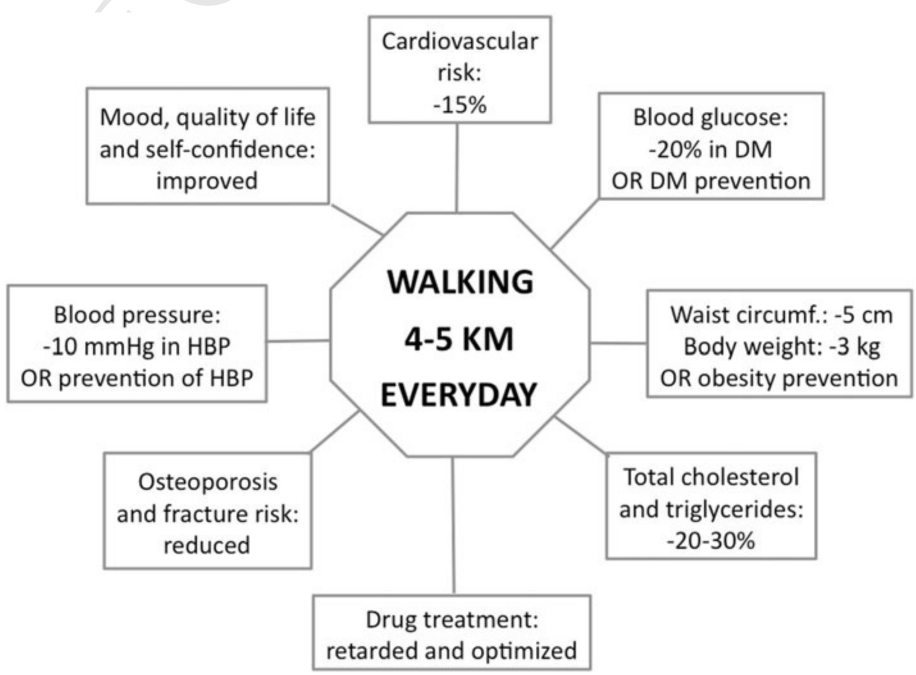

Fig. 1 Benefits of moderate-intensity daily physical activity (e.g., walking) on metabolic disorders. Data combined from a variety of references quoted in the manuscript. *DM* diabetes mellitus, *HBP* high blood pressure

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Conclusions

The beneficial effects of PA in the prevention and treatment of non-communicable diseases clustered around the metabolic syndrome are impressive (Fig. 1), but increasing PA in the population remains difficult [97]. Motivation to exercise and to dietary changes are considerably different and, in most cases, much lower for PA [88]. Data in NAFLD and unpublished data in a large cohort of subjects with T2DM indicate that a large number of cases are either in the pre-contemplation or contemplation stage of change [98], i.e., they do not consider the possibility to engage in PA to improve their disease. The possibility to attain the desired targets of PA in patients requires skills and commitment by physicians, as well as time and willingness by patients [99], but a very low internal fracture (i.e., the discrepancy between the present personal behavior and the desired behavior) acts as a strong barrier against exercise [88]. We need to move from the traditional prescriptive approach to diet and exercising, towards a multidisciplinary intervention, considering that barriers to physical activity may be difficult to overcome in individual cases, and group support may make the difference. Primary care might be the preferred setting to identify patients at risk, but the implementation of PA counseling by GPs remains difficult because of time constraints in busy consulting rooms [100]. We need to develop strategies to facilitate and to disseminate education; the possibility to expand patients' adherence to activity programs by means of information technology is a new area of interest that should be extensively tested in the future. Web-based strategies may indeed represent an opportunity to break down some of the barriers (costs, lack of time, factors objectively limiting spatial and temporal co-presence). A complete integration of these systems, aimed at self-learning (on-line learning without time or space restrictions), collaborative/cooperative learning (forums, virtual communities), and synchronous learning (virtual classrooms, video conferencing, chats) may represent the new frontier to motivate and educate the very large number of people at risk, who cannot attend specialist units.

Conflict of interest None.

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