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

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Physical activity for the prevention and treatment of metabolic 2 disorders 3

Luca Montesi · Simona Moscatiello · 4

- 5 Marcella Malavolti · Rebecca Marzocchi ·
- 6 Giulio Marchesini

7 Received: 12 January 2013/Accepted: 23 April 2013 8 © SIMI 2013

9 Abstract Metabolic syndrome and its various features 10 (obesity, hypertension, dyslipidemia, diabetes, and nonal-11 coholic fatty liver disease) are increasing worldwide and 12 constitute a severe risk for the sustainability of the present 13 universal Italian health care system. Lifestyle interventions 14 should be the first therapeutic strategy to prevent/treat 15 metabolic diseases, far before pharmacologic treatment. 16 The role of diet and weight loss has been fully ascertained, 17 whereas the role of physical activity is frequently over-18 looked both by physicians and by patients. Physical activity 19 has favorable effects on all components of the metabolic 20 syndrome and on the resulting cardiovascular risk, the 21 cornerstone in the development of cardiometabolic dis-22 eases. The quantity and the frequency of physical activity 23 necessary to produce beneficial effects has not been defined 24 as yet, but brisk walking is considered particularly appro-25 priate, as it can be practiced by a large number of indi-26 viduals, without any additional cost, and has a low rate of 27 injury. The effects of exercise and leisure time physical 28 activity extend from prevention to treatment of the various 29 components of the metabolic syndrome, as well as to mood 30 and quality of life. Any effort should be done to favor

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adherence to protocols of physical activity in the	31
community.	32
	33
Keywords Diet · Exercise · Lifestyle · Metabolic	34
syndrome · Physical activity	35

Introduction

The epidemic of metabolic disorders, driven by obesity, 37 constitutes a challenge for health systems worldwide. 38 Several factors are contributing to the increasing preva-39 lence of the various features of the metabolic syndrome 40 (hypertension, dyslipidemia, and type 2 diabetes). Diet and 41 lifestyle have a major role, coupled with genetics. Positive 42 economic developments and better healthcare, favoring 43 population aging, are expected to increase costs to levels 44 no longer sustainable both in Western and in developing 45 countries. For the hundreds of millions worldwide who 46 have the "metabolic syndrome", lifestyle modification is 47 the most appealing approach because of its non-toxicity 48 and high efficacy, compared with medications, and physi-49 50 cal activity (PA) is a fundamental component.

51 It is outside the scope of the present review to discuss 52 the reason(s) and the real existence of the syndrome, i.e., 53 whether a residual risk exists above that conferred by individual features or old and new cardiovascular risk 54 factors [1]. Lifestyle modifications are mandatory for the 55 individual components, and more so when they sum up, not 56 only in the case of overt disease, but also when the indi-57 vidual components are in the range of "pre-disease" (i.e., 58 prediabetes, prehypertension, mild dyslipidemia not 59 requiring drug treatment or low-grade visceral fat accu-60 mulation) [2]. This is the reason for the progressive 61 reduction of the diagnostic cut-offs that occurred along the 62 years (Table 1) (see [3, 4]. 63

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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	ne 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	\geq 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	\geq 150 mg/dL	\geq 150 mg/dL	\geq 150 mg/dL OR on medications	\geq 150 mg/dL	\geq 150 mg/dL OR on medications
Obesity	Waist to hip ratio: >0.9 (men), >0.85 (women); OR BMI ≥30 kg/m ²	WC \geq 94 cm (men), \geq 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	\geq 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

generated by dietary restriction and PA only becomes

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

Hypertension is an independent risk factor for cardiovas-

cular 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,

activity produced additive effects (-10.8 %) [9].

Pre-hypertension/hypertension

This view is supported by a very recent randomized

pivotal for long-term weight loss maintenance [7].

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).

71 Obesity

72 Obesity, namely abdominal obesity, is a well-proven risk 73 factor for coronary heart disease (CHD), whereas PA 74 reduces the risk [5]. Although the significance of over-75 weight and class I obesity on overall mortality has very 76 recently been challenged [6], weight loss is mandatory to 77 reduce cardiovascular risk in obese subjects and any 78 intervention on lifestyle includes PA as necessary compo-79 nent. Limiting the importance of PA to weight loss is, 80 however, reductive; PA is a cornerstone for the treatment 81 of non-communicable disease, independently of weight 82 loss. The amount of calories burned by exercise is probably 83 of minor importance compared with the calorie deficit

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

106 In a systematic review of lifestyle interventions in 107 hypertensive patients, Dickinson et al. [13] found robust 108 evidence for the beneficial effects of a healthy diet, aerobic 109 exercise, alcohol and sodium restriction, and fish oil sup-110 plements. This evidence supports the prescription of a low-111 sodium diet, or of a diet with the characteristics of the Dietary Approaches to Stop Hypertension (DASH) pro-112 gram [14]. The DASH diet, based on the computation of 113 114 servings, was specifically developed to help people prevent 115 or treat hypertension, by reducing the levels of total fat, saturated fat and cholesterol, and increasing potassium, 116 117 calcium, magnesium, fiber, and proteins. Such dietary 118 changes have been shown to reduce blood pressure, mainly 119 systolic BP by 2–14 mmHg in about one month [14], also 120 depending on the amount of weight loss that may produce an additional 5-20 mmHg reduction in systolic BP. In 121 122 subjects with prehypertension or stage-1 hypertension of 123 the PREMIER study, 180 min/week of PA or more, alone 124 or in combination with the DASH diet, significantly redu-125 ces the estimated CHD risk in an 18-month follow-up [15].

126 When superimposed upon dietary changes, exercise per 127 se may reduce both systolic and diastolic pressure by 128 another 5–7 mmHg [16], and exert favorable effects on a 129 variety of cardiovascular risk factors, in a dose-dependent 130 fashion, after correction for confounders [17]. Low levels 131 of cardio-respiratory fitness are associated with a high risk 132 of mortality, and improved fitness is associated with a 133 reduced mortality risk. In a 20-year follow-up of North American women, low physical fitness is associated with a 134 135 20 % increased risk of cardiovascular death for every 136 metabolic equivalent (MET) decrease in exercise capacity 137 [18]. Exercise training produces a graded dose response in 138 fitness in sedentary, overweight, or obese postmenopausal 139 women at moderately high risk of cardiovascular disease 140 [19]. Also moderate levels of fitness induced by exercise 141 are associated with a lower risk for all cause and cardio-142 vascular disease mortality, both in individuals with elevated BP and in those without a diagnosis of hypertension. 143

144 In both normotensive and hypertensive healthy seden-145 tary individuals, any type of exercise (i.e., walking, jog-146 ging, running, and cycling) is beneficial, including 147 resistance training. Walking remains the preferred form of 148 exercise as it may be recommended by healthcare profes-149 sionals to the majority of patients, even the elderly, with 150 few exceptions. A systematic search of the literature 151 identified 27 randomized controlled trials on the effects of 152 walking on blood pressure and nine of them were positive 153 [20]. The beneficial effect on blood pressure control is 154 mainly observed in trials of moderate- to high-intensity 155 walking and of longer duration, suggesting that recom-156 mendations should focus on walking intensity and treatment adherence [20]. Regular walking programs and 157 pedometers for monitoring PA may favor adherence to 158 exercise programs in normotensive, overweight adults. 159 Pedometers may also increase the motivation for PA; they 160 were used to monitor walking programs in 26 studies (8 161 randomized controlled trials and 18 observational studies), 162 where pedometer users significantly increase PA by 26.9 % 163 over baseline. A goal of 10,000 steps/day is necessary to 164 achieve the desired effects, i.e., reduced BP and reduced 165 BMI [21]. In a recent study, walking decreased adjusted 166 mean systolic and diastolic blood pressure by 7–9 % [22]. 167

The PA-induced effects on BP translate into reduced 168 morbidity and mortality in hypertensive patients. When 169 self-reported PA was graded in a prospective, randomized 170 hypertension study (the LIFE study) exercising >30 min 171 twice/weekly is associated with a reduced cardiovascular 172 death, stroke, and myocardial infarction in hypertensive 173 174 patients with left ventricular hypertrophy in a 4.8-year follow-up [23]. Aerobic exercise combined with dietary 175 modification (DASH diet) in sedentary overweight and 176 obese patients with high BP (above the cut-offs for the 177 metabolic syndrome) also improved neurocognitive func-178 tioning [24]. In a short-term trial, aerobic exercise con-179 sisting of moderate-to-vigorous intensity exercise 180 according to current guidelines [25] also reduced both 181 radial and femoral pulse wave velocity [26]. Similarly, 182 exercise training and weight reduction (cycle ergometer 183 training twice a day, 5 days a week, and hypocaloric diet) 184 in patients with drug-treated hypertension reduced BP and 185 cardiovascular risks, and improved abnormal left ventric-186 187 ular relaxation [27].

It is definitely time to move from interventions limited 188 to specialist centers to community-based PA implementa-189 190 tion for the control of hypertension, with the support of new technologies to stimulate adherence. In subjects aged 191 60 and over with mild to moderate hypertension, a 6-month 192 community-based walking intervention based on self-effi-193 cacy theory, including both face-to-face and telephone 194 support designed to assist participants to increase their 195 196 walking, decreases systolic blood pressure by 15 mmHg, with no difference in diastolic pressure [28]. 197

Dyslipidemia

199 Less than optimal lipid and lipoprotein levels, particularly elevated levels of low-density lipoprotein (LDL) choles-200 terol, increase the risk for morbidity and mortality from 201 202 CHD throughout the range of lipid and lipoprotein values [29]. Lifestyle intervention should be the first therapeutic 203 strategy for "cardio-metabolic" patients and international 204 205 agencies recognize regular PA as an essential component 206 of a lifestyle modification program [29].

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207 High levels of PA and cardio-respiratory fitness are 208 associated with reduced risks of morbidity, mortality, and 209 improvement of their prognostic risk factors [30, 31], but 210the optimal intensity or amount of exercise necessary for 211 risk reduction is unknown. As for hypertension, brisk 212 walking is the most commonly suggested type of PA. 213 Current guidelines suggest moderate intensity activity for 214 >30 min/session at least 5 days/week, but there is no 215 definite evidence on the amount of exercise conferring 216 specific health benefits.

217 In sedentary overweight men and women, increasing the 218 amount and intensity of exercise significantly reduces 219 small, dense LDL particles, increases LDL particle size and 220 high-density lipoprotein (HDL) cholesterol, and reduced triglyceride levels. Improvements are neither related to the 222 intensity of exercise or improved fitness, nor to the mini-223 mal weight change, but only to the amount of activity [32]. 224 A meta-analysis of 25 studies including over 1,000 subjects 225 confirms that regular PA reduces the ratio of total to HDL-226 cholesterol (decreasing by about 6 %), as well as the 227 plasma levels of HDL-cholesterol and triglycerides [33], 228 although the latter changes are not statistically significant.

229 The independent effects of exercise intensity and amount 230 have not been conclusively established yet. A systematic 231 review of 28 randomized studies of moderate-to-hard intensity 232 PA for 12 weeks or longer shows a large variability in lipid 233 response, with a significant increase in HDL-cholesterol levels 234 in approximately 40 % of trials [34]. In a more recent trial on sedentary treatment-naïve adults (almost two-thirds women), 235 236 comparing four exercise regimens (moderate vs. hard intensity 237 and low vs. high frequency in a 2×2 model), the hard-238 intensity high-frequency exercise regimen is the only inter-239 vention that produces a significant improvement in HDL cho-240 lesterol compared with physician advice alone, suggesting that 241 both intensity and frequency are important [35]. In a different 242 study [32], the high-intensity high-volume exercise, not the 243 high-intensity low-volume or the low-intensity low-volume 244 exercise over 8 months significantly increases HDL-choles-245 terol level. Thus, changes in HDL may depend on the intensity, 246 frequency, and volume of exercise, and on the individual's 247 baseline level [34]. In a more recent trial [36], patients assigned 248 to high-amount exercise show improvements in HDL size, 249 which are sustained for up to 2 weeks after exercise with-250 drawal. This benefit may be clinically important, as HDL-251 cholesterol particles have anti-inflammatory, antioxidative, 252 anti-platelet, anticoagulant, and pro-fibrinolytic activities, in 253 addition to their role in reverse cholesterol transport. Moreover, 254 moderate-intensity, but not vigorous-intensity, exercise results 255 in a sustained reduction in very low-density lipoprotein 256 (VLDL)-triglycerides over 15 days of detraining.

257 Historically, LDL cholesterol has long been considered a primary risk factor for cardiovascular disease, but the 258 259 multinational INTERHEART study shows that the 291

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apolipoprotein (apo)B/apoA-I ratio is the most important 260 261 modifiable predictor of myocardial infarction [5]. ApoB is a direct measure of the number of atherogenic particles as 262 there is a single apoB molecule present on the surface of all 263 LDL, intermediate density lipoprotein, and VLDL parti-264 cles. ApoA-I is the major protein on HDL particles and 265 thus provides an indication of the number of anti-athero-266 genic particles [37]. Cross-sectional studies associate lower 267 apoB levels with high levels of PA [38] and longitudinal 268 269 studies show that regular exercise reduces apoB by up to 270 20 % [39]. In physically inactive, middle-aged men who are overweight, PA reduces apoB levels as well as the 271 apoB/apoA-I ratio without effect on LDL cholesterol [39]. 272 Finally, in obese and insulin-resistant patients, moderate 273 PA is associated with decreased apoB/apoA-I ratio and 274 275 increased apoA-I, whereas vigorous PA is required to observe a reduction in apoB [40], after adjustment for 276 smoking, systolic blood pressure, and waist circumference. 277

In summary, PA has a remarkable effect on the lipid 278 profile, one of the most relevant modifiable risk factors for 279 CHD morbidity and mortality. This conclusion has, how-280 ever, been challenged by a very recent paper showing that 281 objectively measured sedentary time is the most important 282 283 lifestyle factor associated with a poor metabolic profile (altered triglycerides, HDL-cholesterol, glucose) after 284 adjustment for BMI and moderate-to-vigorous physical 285 activity [41]. These data further indicate the importance of 286 287 implementing leisure-time PA in the community to reduce the burden of metabolic diseases, as sedentary behavior, 288 per se, is associated with increased cardiovascular mor-289 290 tality [42].

Prediabetes/diabetes

There is strong evidence that the occurrence of both pre-292 diabetes and type 2 diabetes (T2DM) is strictly associated 293 294 with low cardio-respiratory fitness. In a seminal report of the Nurses' Health Study, Hu et al. [43] report that the 295 relative risk of developing T2DM is reduced across quin-296 297 tiles of time spent per week on each of eight common PAs, including walking, during an 8-year follow-up (over half 298 million person-years). Faster than usual walking pace is 299 independently associated with decreased risk, but equiva-300 lent energy expenditures similarly promoted risk reduction. 301 302 Several clinical trials confirm that PA is an effective tool for the prevention and management of altered glucose 303 metabolism. 304

Prevention studies (Table 2)

Four large-scale, multi-centre, randomized clinical trials 306 are the corner stones in the evidence of the benefits of PA 307

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Study (Ref.)	No. Pz.	Arms	Objectives	Study duration and follow-up	Results
Finnish Diabetes Prevention Study [45, 50]	522	Intensive lifestyle Control	Weight loss $\geq 5 \%$ Total intake of fat <30 % Saturated fat <10 % Intake of fiber $\geq 15 \%$ 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

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

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

308 in a prediabetic population. The US Diabetes Prevention 309 Program (DPP) reports a 58 % reduction in the incidence 310 of T2DM after an average of 2.8 years of lifestyle inter-311 vention aimed at 150 min/week of moderate-intensity PA 312 and dietary restriction to induce a 7 % weight loss [44]. A 313 perfectly identical risk reduction of 58 % is associated with 314 lifestyle changes in the Finnish Diabetes Prevention Study 315 (DPS) [45]. In Asian Indians with impaired glucose toler-316 ance (IGT), lifestyle modifications, including 210 min/ week of brisk walking and dietary modifications, reduces 317 the risk of incident diabetes by 28 % [46], whereas the 318 Chinese Da Qing study demonstrates a risk reduction of 319 incident diabetes of 31, 46, and 42 %, respectively, in 320 subjects with IGT in a follow-up of 6 years of three 321 intervention groups (diet only, exercise only, and diet plus 322 exercise), independent of obesity [47]. Long-term follow-323 ups of these studies confirm that systematic interventions to 324 improve lifestyle habits maintain the beneficial effects up 325

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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 reduction346across BMI categories, in the presence and absence of347visceral adiposity, confirming that PA prevents T2DM348regardless of adiposity and weight loss.349

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]. 354

Intervention studies	(Table 3)		
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The beneficial effects of PA and improved cardiorespira-356 tory fitness on metabolic control in T2DM finds support in 357 the Look AHEAD (Action for Health in Diabetes) study. 358 This multicenter randomized controlled trial of over 5,000 359 overweight or obese people with T2DM transposed the 360 general framework of the Diabetes Prevention Program in 361 the field of intervention. An intensive lifestyle intervention 362 (ILI), aimed at achieving and maintaining a weight loss of 363

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) vs0.88 (DSE) Fitness: +12.7 vs. +1.9 % HbA1c: -0.36 % (ILI) vs0.09 % (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/m² 	1 year	Results at 1 year: HbA1c: -0.49 % (EXE) vs0.10 % (control) Improvement in blood pressure and dyslipidemia (EXE) Increase in VO ₂ max (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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364 7 % through diet and increased PA (175 min/week) was 365 compared with standard education. The primary endpoint 366 of the study was a composite outcome consisting of inci-367 dent cardiovascular events, to be tested after a programmed 368 follow-up of 13.5 years. The results at 12- and 48-month 369 follow-up in over four thousand individuals are encourag-370 ing: subjects who completed the 1-year trial improve their 371 cardiorespiratory fitness (assessed using a sub-maximal 372 graded exercise test) [56], after adjustment for baseline 373 fitness (20.9 % in ILI vs. 5.7 %; P < 0.001) and also a 374 modest weight loss (5-10 %) is associated with improved 375 cardiovascular risk factors. These benefits are partly maintained at 4 years [57]. However, a very recent re-376 377 analysis of ongoing data showed that the expected differ-378 ences in cardiovascular outcome could no longer be 379 attained and the study was terminated because of futility on 380 October 2012. Termination was unexpected, also consid-381 ering that the study had shown remission of diabetes in up 382 to 10 % of treated cases in the ILI group, compared with 383 1-2 % in the standard care group [58].

384 In the Italian setting, Di Loreto et al. [59] show that 385 2 years of regular aerobic exercise in a diabetic population 386 reduces all aspects of the metabolic syndrome. Any graded 10 MET-h/week of PA (corresponding to a 30-min walk/ 387 388 day), after a course of structured PA, reduces BMI and 389 improves HbA1c [60]. Of note, in the intervention group, 390 drug treatment, and the overall direct cost of diabetes are 391 reduced in parallel with decreased estimated 10-year cor-392 onary risk [59].

393 Also the type and mode of PA can make a difference. In 394 the Italian Diabetes and Exercise Study (IDES) an ILI 395 based on planned and supervised, mixed exercise (aerobic 396 and resistance training) improved HbA1c and reduced the 397 cardiovascular risk [61]. The intensive program of 398 150 min/week in two divided sessions of aerobic and 399 resistance exercise supervised by a trainer, associated with 400 dedicated counseling produced significant benefits in a 401 12-month follow-up; patients started exercising also out-402 side gym sessions [61] and their quality of life improved 403 systematically in relation to the attained PA volume. In a 404 pre-specified analysis of the IDES cohort, the benefits of 405 PA/exercise are once again independent of weight loss 406 [62], and in low-fitness, sedentary individuals with T2DM, 407 increasing exercise intensity was not harmful, but did not 408 provide additional benefits on cardiovascular risk factors 409 [63]. The benefits of resistance exercise were confirmed in 410 the RAED2 study [64] and in insulin-treated T2DM [65].

411 Nonalcoholic fatty liver disease (NAFLD)

412 Non-alcoholic fatty liver disease is characterized by liver413 triglyceride accumulation (steatosis) in subjects with no

history of excessive alcohol intake. NAFLD encompasses a 414 415 large histological spectrum, from simple steatosis, to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, 416 potentially progressing to hepatocellular carcinoma [66]. It 417 is the most common cause of chronically elevated liver 418 419 enzymes and chronic liver disease, affecting 20-35 % of the general adult population in the Western countries. 420 Although the prevalence is higher in the age group between 421 40 and 70 years, NAFLD is present in almost all age ran-422 ges, including the pediatric population, with a prevalence 423 of ~ 10 % in children and adolescents, which is expected 424 to rise sharply as an effect of the growing epidemic of 425 obesity in childhood and adolescence [67]. 426

NAFLD is regarded as the hepatic expression of the 427 metabolic syndrome, considering its close association with 428 429 all its components [66, 68], similar pathophysiological mechanisms based on insulin resistance [69], and a similar 430 cardiovascular risk [70]. Liver fat is indeed associated with 431 a diffuse cardiovascular involvement (increased intima-432 media thickness and the presence of carotid plaques), 433 independently of the presence of T2DM, and by endothelial 434 dysfunction [71]; the outcome is strictly dependent on 435 cardiovascular events [72], adding to liver-associated 436 morbidity and mortality, as well as to cancer mortality [73]. 437

In the absence of specific pharmacological treatments 438 and considering the strong association between NAFLD, 439 metabolic syndrome, insulin resistance and other metabolic 440 441 abnormalities [74], prevention and treatment are mainly directed at improving insulin sensitivity and at correcting 442 cardiometabolic risk factors [66, 75]. These objectives are 443 444 achieved through a first-level intervention that consists in lifestyle change, calorie restriction, and increased PA. PA 445 is expected to achieve these objectives, independently of 446 weight loss [76, 77]. The beneficial effects of exercise on 447 liver steatosis and biochemical tests became clinically 448 449 significant after a very short-term program of aerobic exercise (treadmill walking for 60 min/day on 7 consecu-450 tive days at 85 % of maximal heart rate): the biochemical 451 452 profile is improved, the markers of hepatocyte apoptosis are reduced, and the whole body fat oxidation is increased 453 [78]. Exercise programs of longer duration (4 weeks to 454 6 months) generate additional benefits and reduce the 455 intrahepatic triglyceride content [77, 79], serum amino-456 transferase levels [80], insulin resistance [81, 82], and even 457 improve the histological pattern (NAS score at liver 458 459 biopsy) [83] in relation to changes in body weight or body composition [83]. These benefits are also demonstrated in 460 adolescents [84]. However, no study has so far demon-461 strated a significant effect of behavior treatment (including 462 PA implementation) on hard outcomes, including mortal-463 ity, cardiovascular events, or progression to cirrhosis. 464

Individual reports of exercise interventions often have 465 low sample sizes and insufficient power to detect clinically 466

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467 meaningful hepatic benefits and most of them include 468 contemporary dietary counseling, which does not allow an 469 independent evaluation of PA. In general, there are no 470 accepted criteria for the optimal intensity, duration, or total 471 volume of exercise to obtain these beneficial effects and the 472 meta-analysis can only be used to substantiate the 'global 473 benefit' of exercise therapy on liver fat. In a systematic 474 review with meta-analysis on the efficacy of exercise 475 interventions (from 2- to 24-week duration, exercise on 476 2-6 days/week, intensity 45-85 % of VO₂ peak), Keating 477 et al. [85] found six studies directly comparing exercise vs. 478 a non-exercise control arm on liver fat and serum ALT in 479 adults. In 6/12 selected studies, the results favor exercise. 480 By pooling the data (156 adults, mostly overweight or obese), there is clear evidence for a systematic benefit of 482 exercise on liver fat, with minimal or no weight loss. There 483 is no effect on serum ALT levels, which are normal at 484 baseline in several reports. In addition, PA improves car-485 diovascular risk factors including hypertension, T2DM, 486 dyslipidemia, visceral adiposity and reduces the absolute 487 cardiovascular risk [85]. In a cross-sectional analysis of 488 subjects enrolled in the US NASH Clinical Research Net-489 work, only vigorous exercise, not moderate exercise, nor 490 total duration or volume of PA, are associated with 491 decreased odds of having NASH or advanced fibrosis [86]. 492 The biological basis for this difference is unknown.

493 In conclusion, the intensity of PA/exercise may be an 494 important dimension to consider when counseling patients 495 and planning interventions. Intervention studies with 496 objective measures of PA are required to confirm the dif-497 ferential effects of vigorous compared with moderate PA 498 on NAFLD severity [87]. At present, experts recommend 30 min of moderate intensity PA on most days of the week 499 500 [81], or vigorous-intensity PA \geq 3 times per week for \geq 20 min each time [87]. Implementation of PA remains the 501 more demanding challenge because there is evidence that 502 counseling about the benefits of exercise or exercise pre-503 504 scription does not translate into positive outcomes [81].

A lot of psychological and physical barriers reduce 505 adherence to PA in NAFLD, and motivation may be low in 506 most cases [88]. NAFLD subjects are characterized by a 507 508 sedentary lifestyle [89, 90], also due to physical factors 509 objectively limiting exercise, such as fatigue [91], reduced cardiorespiratory fitness [90, 92], osteoarthritis linked with 510 obesity and associated cardiovascular disease. From phy-511 sicians' perspectives, the barriers to promote exercise as 512 therapy for NAFLD are the scarce confidence with edu-513 514 cational programs, lack of training in communication and group management, the awareness of future scarce adher-515 ence of patients, and their high dropout rate from lifestyle 516 interventions [93]; from patients' perspectives, barriers 517 include climate factors, perceived effort of exercise and 518 519 lack of time, as well as lack of self-efficacy [94]. A structured program of cognitive behavioral therapy may 520 favor lifestyle changes, increasing the probability to reduce 521 522 body weight, to normalize liver enzymes, and to reduce the number of features of the metabolic syndrome [95]. 523

In conclusion, as with other chronic diseases related to 524 525 unhealthy behaviors, we need a global strategy to reduce the 526 burden of NAFLD [96]. Interventions should include strategies to promote regular contacts with a health care professional, 527 self-monitoring, and individual goal setting, considering the 528 529 large differences present in the community. This is the way to disseminate PA in a sedentary population [81]. 530

Fig. 1 Benefits of moderate-Cardiovascular intensity daily physical activity risk: (e.g., walking) on metabolic disorders. Data combined from -15% Mood, quality of life Blood glucose: a variety of references quoted in and self-confidence: -20% in DM the manuscript. DM diabetes improved **OR DM prevention** mellitus, HBP high blood pressure WALKING Blood pressure: Waist circumf .: -5 cm 4-5 KM -10 mmHg in HBP Body weight: -3 kg OR prevention of HBP OR obesity prevention EVERYDAY Total cholesterol Osteoporosis and triglycerides: and fracture risk: -20-30% reduced Drug treatment: retarded and optimized

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531 Conclusions

532 The beneficial effects of PA in the prevention and treat-533 ment of non-communicable diseases clustered around the 534 metabolic syndrome are impressive (Fig. 1), but increasing 535 PA in the population remains difficult [97]. Motivation to 536 exercise and to dietary changes are considerably different 537 and, in most cases, much lower for PA [88]. Data in NA-538 FLD and unpublished data in a large cohort of subjects 539 with T2DM indicate that a large number of cases are either 540 in the pre-contemplation or contemplation stage of change 541 [98], i.e., they do not consider the possibility to engage in 542 PA to improve their disease. The possibility to attain the 543 desired targets of PA in patients requires skills and com-544 mitment by physicians, as well as time and willingness by 545 patients [99], but a very low internal fracture (i.e., the 546 discrepancy between the present personal behavior and the 547 desired behavior) acts as a strong barrier against exercise 548 [88]. We need to move from the traditional prescriptive 549 approach to diet and exercising, towards a multidisciplin-550 ary intervention, considering that barriers to physical 551 activity may be difficult to overcome in individual cases, 552 and group support may make the difference. Primary care 553 might be the preferred setting to identify patients at risk, 554 but the implementation of PA counseling by GPs remains 555 difficult because of time constraints in busy consulting 556 rooms [100]. We need to develop strategies to facilitate and 557 to disseminate education; the possibility to expand 558 patients' adherence to activity programs by means of 559 information technology is a new area of interest that should 560 be extensively tested in the future. Web-based strategies 561 may indeed represent an opportunity to break down some 562 of the barriers (costs, lack of time, factors objectively 563 limiting spatial and temporal co-presence). A complete 564 integration of these systems, aimed at self-learning (on-line 565 learning without time or space restrictions), collaborative/ 566 cooperative learning (forums, virtual communities), and 567 synchronous learning (virtual classrooms, video confer-568 encing, chats) may represent the new frontier to motivate 569 and educate the very large number of people at risk, who 570 cannot attend specialist units.

571 Conflict of interest None.

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