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

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5 **Marcella Malavolti · Rebecca Marzocchi ·**
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11 coholic fatty liver disease) are increasing worldwide and
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29 components of the metabolic syndrome, as well as to mood
30 and quality of life. Any effort should be done to favor

adherence to protocols of physical activity in the 31
community. 32

Keywords Diet · Exercise · Lifestyle · Metabolic 34
syndrome · Physical activity 35

Introduction 36

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
cal activity (PA) is a fundamental component. 50

It is outside the scope of the present review to discuss 51
the reason(s) and the real existence of the syndrome, i.e., 52
whether a residual risk exists above that conferred by 53
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	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	$\geq 140/90$ mmHg	$\geq 140/90$ mmHg	$\geq 130/85$ mmHg OR on medications	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg 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

64 We discuss the evidence supporting a major role for PA
65 both in the prevention and treatment of metabolic disor-
66 ders, over and above the effects on weight loss. For the
67 individual components of the metabolic syndrome, the data
68 on hard outcomes (mortality and cardiovascular events)
69 will be separated from the effects on surrogate markers
70 (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

generated by dietary restriction and PA only becomes 84
pivotal for long-term weight loss maintenance [7]. 85

This view is supported by a very recent randomized 86
controlled trial (RCT), comparing the effects of diet, 87
exercise, or the combination of diet and exercise [8]. 88
Exercise significantly improved the functional status, 89
without any effect on body weight; diet significantly 90
reduced body weight, whereas combination treatment more 91
significantly improved physical performance. Similarly, in 92
postmenopausal women, diet was more effective than a 93
physical activity program on weight loss at 1 year (-8.5 94
vs. -2.4 %), but the combination of diet + physical 95
activity produced additive effects (-10.8 %) [9]. 96

Pre-hypertension/hypertension 97

Hypertension is an independent risk factor for cardiovas- 98
cular disease and a relationship exists between blood 99
pressure (BP) levels and CHD [5] in spite of remarkable 100
advances in therapy [10]. Drug-treated hypertensive 101
patients are still at risk for future cardiac events [11] and 102
behavior therapy, including healthy diet and increased PA, 103

104 remains the background approach because of its beneficial
105 effects 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
112 Dietary Approaches to Stop Hypertension (DASH) pro-
113 gram [14]. The DASH diet, based on the computation of
114 servings, was specifically developed to help people prevent
115 or treat hypertension, by reducing the levels of total fat,
116 saturated fat and cholesterol, and increasing potassium,
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
121 an additional 5–20 mmHg reduction in systolic BP. In
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
134 American women, low physical fitness is associated with a
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 ele-
143 vated BP and in those without a diagnosis of hypertension.

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

157 treatment adherence [20]. Regular walking programs and
158 pedometers for monitoring PA may favor adherence to
159 exercise programs in normotensive, overweight adults.
160 Pedometers may also increase the motivation for PA; they
161 were used to monitor walking programs in 26 studies (8
162 randomized controlled trials and 18 observational studies),
163 where pedometer users significantly increase PA by 26.9 %
164 over baseline. A goal of 10,000 steps/day is necessary to
165 achieve the desired effects, i.e., reduced BP and reduced
166 BMI [21]. In a recent study, walking decreased adjusted
167 mean systolic and diastolic blood pressure by 7–9 % [22].

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

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

198 Dyslipidemia

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

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
 210 the 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
 221 triglyceride levels. Improvements are neither related to the
 222 intensity of exercise or improved fitness, nor to the minimal
 223 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
 235 sedentary treatment-naïve adults (almost two-thirds women),
 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 drawl. 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
 258 a primary risk factor for cardiovascular disease, but the
 259 multinational INTERHEART study shows that the

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

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

291 Prediabetes/diabetes

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

305 Prevention studies (Table 2)

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

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 $\geq 5\%$ 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 $\geq 7\%$ ≥ 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

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
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

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

330 All these studies were carried out adding nutritional
331 modification/counseling to PA. A recent prospective cohort
332 study observed the effects of a 6-month program based on
333 exercise only (300 min/week of moderate-intensity exer-
334 cise) in a large group of Korean subjects with normal or
335 impaired fasting glucose [53]. During a 2-year follow-up,
336 regular exercise is associated with a 23 % risk reduction of
337 incident T2DM, particularly in subjects with overweight/
338 obesity, where reduced waist circumference and BMI are
339 associated with reduced fasting glucose levels. These
340 results are in keeping with the hypothesis that regular
341 exercise might prevent diabetes via reduced obesity or
342 body fat redistribution, a conclusion not fully supported by
343 obesity studies [8]. The EPIC-InterAct case-cohort study
344 specifically addressed the relative role of PA and weight
345 loss on incident T2DM in men and women [54]. Higher

346 levels of PA are associated with a significant risk reduction
347 across BMI categories, in the presence and absence of
348 visceral adiposity, confirming that PA prevents T2DM
349 regardless of adiposity and weight loss.

350 Based on the above evidence, health agencies recom-
351 mend at least 150 min/week of moderate to vigorous aer-
352 obic-based exercise to prevent T2DM, but we need to move
353 from a prescriptive model to a comprehensive battle
354 against sedentary lifestyle [41, 55].

Intervention studies (Table 3)

355
356 The beneficial effects of PA and improved cardiorespira-
357 tory fitness on metabolic control in T2DM finds support in
358 the Look AHEAD (Action for Health in Diabetes) study.
359 This multicenter randomized controlled trial of over 5,000
360 overweight or obese people with T2DM transposed the
361 general framework of the Diabetes Prevention Program in
362 the field of intervention. An intensive lifestyle intervention
363 (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 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, VO₂ oxygen consumption, WL weight loss

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
 376 maintained at 4 years [57]. However, a very recent re-
 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
 387 10 MET-h/week of PA (corresponding to a 30-min walk/
 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 IDDES 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 liver
 413 triglyceride accumulation (steatosis) in subjects with no

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

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

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

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

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
 481 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.

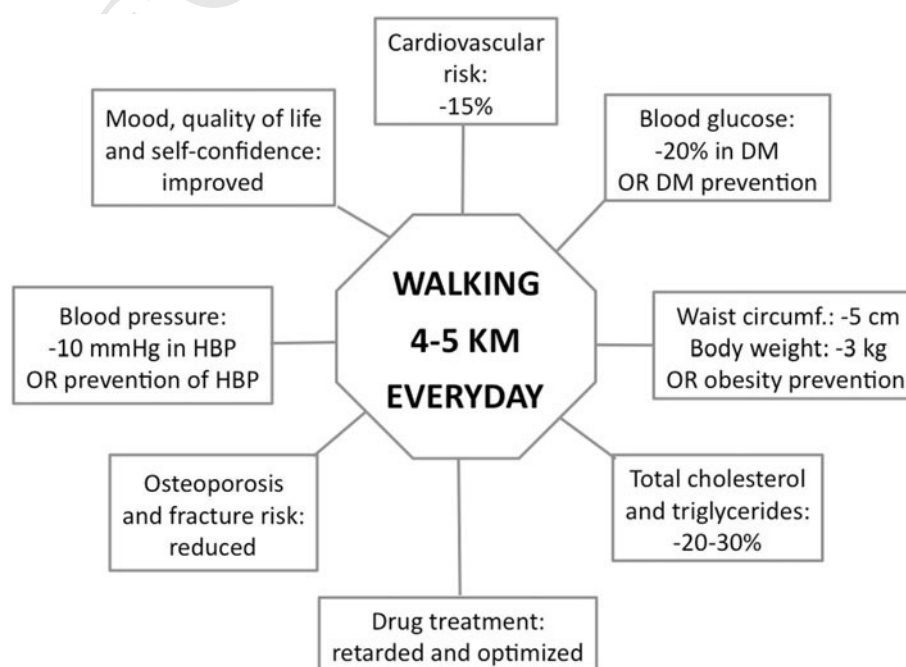
493 In conclusion, the intensity of PA/exercise may be an
 494 important dimension to consider when counseling patients
 495 and planning interventions. Intervention studies with
 496 objective measures of PA are required to confirm the dif-
 497 ferential effects of vigorous compared with moderate PA
 498 on NAFLD severity [87]. At present, experts recommend

30 min of moderate intensity PA on most days of the week
 [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 pre-
 scription 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 phy-
 sicians' perspectives, the barriers to promote exercise as
 therapy for NAFLD are the scarce confidence with edu-
 cational programs, lack of training in communication and
 group management, the awareness of future scarce adher-
 ence 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



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 multidisciplinary
 550 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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