# Effect of an Intensive Exercise Intervention Strategy on Modifiable Cardiovascular Risk Factors in Subjects With Type 2 Diabetes Mellitus

## *A Randomized Controlled Trial: The Italian Diabetes and Exercise Study (IDES)*

*Stefano Balducci, MD; Silvano Zanuso, PhD; Antonio Nicolucci, MD; Pierpaolo De Feo, MD, PhD; Stefano Cavallo, PhD; Patrizia Cardelli, PhD; Sara Fallucca, PhD; Elena Alessi, MD; Francesco Fallucca, MD; Giuseppe Pugliese, MD, PhD; for the Italian Diabetes Exercise Study (IDES) Investigators*

**Background:** This study aimed to assess the efficacy of an intensive exercise intervention strategy in promoting physical activity (PA) and improving hemoglobin $A_{1c}$ ($HbA_{1c}$) level and other modifiable cardiovascular risk factors in patients with type 2 diabetes mellitus (T2DM).

**Methods:** Of 691 eligible sedentary patients with T2DM and the metabolic syndrome, 606 were enrolled in 22 outpatient diabetes clinics across Italy and randomized by center, age, and diabetes treatment to twice-a-week supervised aerobic and resistance training plus structured exercise counseling (exercise group) vs counseling alone (control group) for 12 months. End points included $HbA_{1c}$ level (primary) and other cardiovascular risk factors and coronary heart disease risk scores (secondary).

**Results:** The mean (SD) volume of PA (metabolic equivalent hours per week) was significantly higher ($P<.001$) in the exercise (total PA [nonsupervised conditioning PA + supervised PA], 20.0 [0.9], and nonsupervised, 12.4 [7.4]) vs control (10.0 [8.7]) group. Compared with the control group, supervised exercise produced significant improvements (mean difference [95% confidence interval]) in physical fitness; $HbA_{1c}$ level (–0.30% [–0.49% to –0.10%]; $P<.001$); systolic (–4.2 mm Hg [–6.9 to –1.6 mm Hg]; $P=.002$) and diastolic (–1.7 mm Hg [–3.3 to –1.1 mm Hg]; $P=.03$) blood pressure; high-density lipoprotein (3.7 mg/dL [2.2 to 5.3 mg/dL]; $P<.001$) and low-density lipoprotein (–9.6 mg/dL [–15.9 to –3.3 mg/dL]; $P=.003$) cholesterol level; waist circumference (–3.6 cm [–4.4 to –2.9 cm]; $P<.001$); body mass index; insulin resistance; inflammation; and risk scores. These parameters improved only marginally in controls.

**Conclusions:** This exercise intervention strategy was effective in promoting PA and improving $HbA_{1c}$ and cardiovascular risk profile. Conversely, counseling alone, though successful in achieving the currently recommended amount of activity, was of limited efficacy on cardiovascular risk factors, suggesting the need for a larger volume of PA in these high-risk subjects.

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CARDIORESPIRATORY FITness is inversely related to all-cause and cardiovascular mortality, both in normal subjects and those with cardiovascular disease and cardiovascular risk factors,[1] including type 2 diabetes mellitus (T2DM).[2,3] A low level of physical activity (PA) is also associated with increased prevalence of T2DM[4] and the metabolic syndrome.[5] Conversely, in patients with T2DM, a moderate-high level of PA was associated with reduced total and cardiovascular mortality,[6,7] and a lifestyle intervention to achieve and maintain weight loss through decreased caloric intake and increased PA improved glycemic control and cardiovascular risk factors.[8] Lifestyle modification programs including PA were also shown to prevent development of T2DM[9,10] and to improve cardiovascular risk factors[11] in subjects with impaired glucose tolerance (IGT).

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The US Department of Health and Human Services[12] and the American College of Sports Medicine[13] recommend a minimum of 150 min/wk of moderate-intensity or, in moderately fit subjects, 60 min/wk of vigorous exercise or PA. The American Diabetes Association has extended these prescriptions also to subjects with IGT, to prevent T2DM development, and to patients with T2DM, to improve glycemic control, assist with weight maintenance, and reduce cardiovascular risk.[14] However, it is debatable whether the same volume of PA

**Author Affiliations** are listed at the end of this article.
**Group Information:** The IDES Investigators and Diabetes and Metabolic Fitness Centers are listed on page 1802.

could be applied to subjects with T2DM, who have a high cardiovascular risk. It is also essential to identify effective strategies to promote an adequate amount of PA in these subjects. Counseling interventions have been recently designed and tested successfully in clinical settings[15] and those focused only on exercise and PA appear to be more effective than those targeting multiple behaviors.[16] Moreover, meta-analyses of small-sized studies showed that supervised exercise is effective in improving cardiorespiratory fitness,[17] glycemic control,[18] and other cardiovascular risk factors.[19] Finally, growing evidence suggests that resistance training is beneficial also in diabetic patients, and a recent trial showed that combined aerobic and resistance exercise is more effective than either one alone.[20]

The aim of the Italian Diabetes and Exercise Study (IDES) was to assess whether a strategy combining a prescribed and supervised mixed (aerobic and resistance) training program with structured exercise counseling is effective in promoting PA and improving hemoglobin $A_{1c}$ ($HbA_{1c}$) level and other modifiable cardiovascular risk factors in a large cohort of sedentary subjects with T2DM. This combined strategy was compared with conventional disease management, including exercise counseling.

## METHODS

### PARTICIPANTS

This randomized controlled trial was conducted in 22 outpatient diabetes clinics across Italy, each connected with a Metabolic Fitness Center. In these gym facilities, patients trained under the supervision of an exercise specialist. The research protocol was approved by the locally appointed ethics committees, and participants gave written informed consent. To improve efficacy and safety of exercise intervention and patient adherence, a specific strategy was implemented prior to starting the IDES for training and selecting a group of diabetologists and exercise specialists to provide exercise prescription and counseling and supervise exercise sessions, respectively (eAppendix 1; http://www.archinternmed.com).

This study enrolled sedentary patients with T2DM fulfilling the International Diabetes Federation (IDF) criteria for the metabolic syndrome,[21] which is almost invariably associated with T2DM and contributes significantly to the increased cardiovascular risk of these subjects.[22] Patients having any condition limiting or contraindicating PA were excluded from the study. Design and methods have been detailed elsewhere.[23]

### RANDOMIZATION AND INTERVENTIONS

Between October 1, 2005, and March 31, 2006, of 691 eligible patients, 606 were recruited and randomized to supervised training plus structured exercise counseling (exercise [EXE] group, n=303) vs counseling alone as part of standard care (control [CON] group, n=303) for 12 months (**Figure 1**). Randomization was stratified by center and, within each center, by age (<60 vs ≥60 years) and type of diabetes treatment (diet±oral agents vs insulin), using a permuted-block randomization software program installed in a computer at each participating center. The allocation sequence was generated by the coordinating center and was concealed until interventions were assigned. Physicians and patients were not blinded to group assignment, whereas sample blinding at central laboratory was achieved using bar codes.

Standard care consisted of a treatment regimen aimed at achieving optimal glycemic, lipid, blood pressure (BP), and body

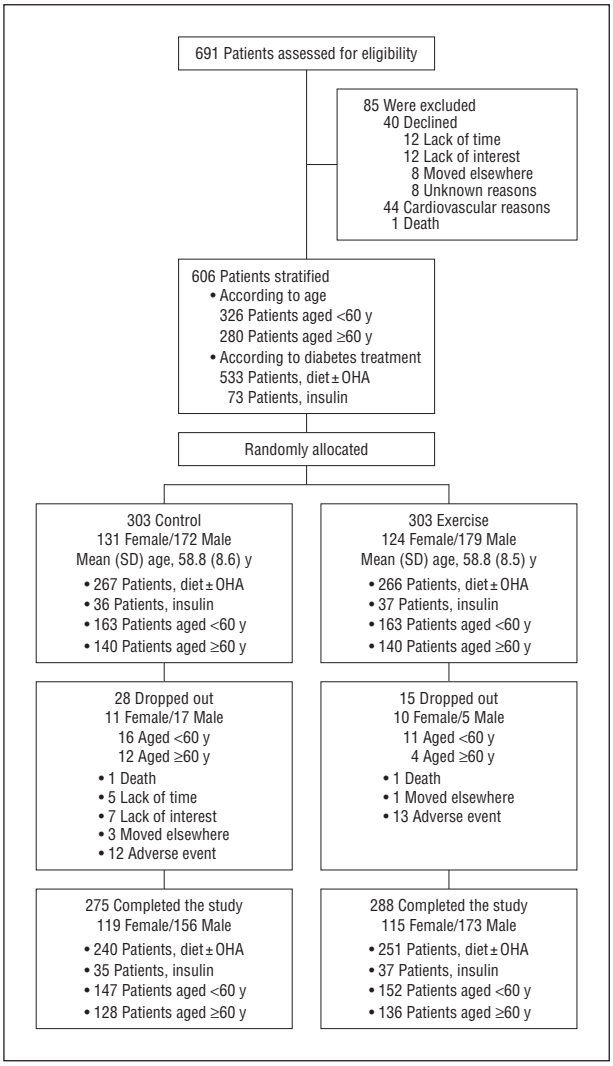


**Figure 1.** Study flow diagram. OHA indicates oral hypoglycemic agent.

weight targets, as established by current guidelines, and included glucose-, lipid-, and BP-lowering agents as needed.[23] For ethical reasons, drugs were also adjusted throughout the study to attain target levels and to account for reduced needs. Since all patients were overweight or obese, caloric intake (55% complex carbohydrates, 30% fat, and 15% protein) was reduced to obtain a negative balance of 500 kcal/d against energy expended. Requirements were calculated by adding the estimated energy expenditure from PA to basal metabolism.[23] Adherence to diet was verified by the use of food diaries, and dietary prescriptions were adjusted at each intermediate visit.

Subjects from both groups received a structured individualized counseling,[15] aimed at achieving the currently recommended amount of PA by encouraging any type of commuting, occupational, home, and leisure time PA. Counseling was reinforced every 3 months.

The training program for the EXE group consisted of 150 min/wk in 2 supervised sessions of progressive mixed (aerobic and resistance) training.[23] Aerobic training was performed using treadmill, step, elliptical, arm, or cycle ergometer. Exercise load for each equipment was calculated to achieve prescribed exercise intensity, expressed as percentage of maximal oxygen consumption ($\dot{V}O_{2max}$), by the use of standard equations.[24] Resistance training consisted of 4 resistance exercises, ie, thrust movement on the transverse plane (chest press or

**Table 1. Volume of Physical Activity (PA), Fitness, Anthropometric, and Biochemical Parameters and Medications at Baseline and at the End of the 12-Month Study Period[a]**

| Variable | CON Baseline | CON 12 mo | *P* Value, 0-12 mo[b] | EXE Baseline | EXE 12 mo | *P* Value, 0-12 mo[b] | Mean Difference (95% CI) | *P* Value, EXE vs CON[c] |
|---|---|---|---|---|---|---|---|---|
| Nonsupervised PA, MET-h/wk | | | | | | | | |
| Conditioning | 0.76 (1.5) | 10.0 (8.7) | <.001 | 0.73 (1.8) | 12.5 (7.4) | <.001 | 2.47 (1.1 to 3.8) | <.001 |
| Nonconditioning | NA | 6.7 (4.2) | NA | NA | 6.6 (3.8) | NA | −0.16 (−0.82 to 0.50) | .60 |
| Supervised PA, MET-h/wk | NA | NA | NA | NA | 7.6 (2.8) | NA | NA | NA |
| Total PA, MET-h/wk[d] | 0.76 (1.5) | 10.0 (8.7) | <.001 | 0.73 (1.8) | 20.0 (9.0) | <.001 | 10.0 (8.6 to 11.5) | <.001 |
| Estimated $\dot{V}O_{2max}$, mL/kg/min | 25.9 (7.0) | 27.5 (6.8) | <.001 | 25.9 (5.4) | 30.4 (5.8) | <.001 | 2.8 (2.1 to 3.5) | <.001 |
| Upper body strength, kg | 39.7 (15.7) | 39.1 (15.6) | .94 | 40.2 (16.3) | 51.0 (19.0) | <.001 | 11.0 (9.5 to 12.5) | <.001 |
| Lower body strength, kg | 104.0 (69.5) | 102.3 (65.9) | .12 | 108.0 (64.5) | 139.8 (72.8) | <.001 | 30.8 (25.1 to 35.6) | <.001 |
| Bending, cm | 11.2 (9.6) | 10.1 (10.3) | <.001 | 12.5 (9.9) | 6.7 (9.4) | <.001 | −4.6 (−5.7 to −3.6) | <.001 |
| $HbA_{1c}$, % | 7.15 (1.4) | 7.02 (1.2) | .48 | 7.12 (1.4) | 6.70 (1.1) | <.001 | −0.30 (−0.49 to −0.10) | <.001 |
| Fasting blood glucose, mg/dL | 150 (52) | 140 (47) | .005 | 145 (49) | 135 (42) | <.001 | −0.68 (−9.4 to 8.1) | .88 |
| Serum insulin, μU/mL | 12.8 (8.6) | 12.9 (6.9) | .06 | 12.4 (8.1) | 11.3 (7.4) | .001 | −1.18 (−2.36 to 0.0) | <.001 |
| HOMA-IR | 4.8 (3.9) | 4.5 (3.1) | .29 | 4.5 (3.6) | 3.8 (2.9) | <.001 | −0.36 (−0.94 to 0.22) | .047 |
| SBP, mm Hg | 142 (18) | 138 (16) | .001 | 140 (18) | 132 (14) | <.001 | −4.2 (−6.9 to −1.6) | .002 |
| DBP, mm Hg | 85 (10) | 83 (9) | .02 | 84 (10) | 80 (8) | <.001 | −1.7 (−3.3 to −1.1) | .03 |
| TG, mg/dL | 139 (81) | 141 (74) | .11 | 131 (97) | 132 (82) | .20 | −6.7 (−14.4 to 11.8) | .85 |
| TC, mg/dL | 201 (34) | 188 (36) | <.001 | 199 (32) | 181 (35) | <.001 | −5.3 (−12.0 to 1.4) | .12 |
| HDL-C, mg/dL | 45.8 (10.5) | 45.6 (10.0) | .65 | 44.9 (11.4) | 48.4 (11.9) | <.001 | 3.7 (2.2 to 5.3) | <.001 |
| LDL-C, mg/dL | 128 (34) | 114 (33) | <.001 | 129 (31) | 106 (29) | <.001 | −9.6 (−15.9 to −3.3) | .003 |
| Waist circumference, cm | 105.1 (11.0) | 104.8 (10.9) | .04 | 105.2 (11.8) | 101.3 (11.4) | <.001 | −3.6 (−4.4 to −2.9) | <.001 |
| BMI | 31.9 (4.6) | 31.7 (4.5) | .20 | 31.2 (4.6) | 30.3 (4.4) | <.001 | −0.78 (−1.07 to −0.49) | <.001 |
| hs-CRP, mg/L | 2.6 (2.0) | 2.8 (2.2) | .20 | 2.8 (2.2) | 2.0 (1.9) | <.001 | −1.0 (−1.4 to −0.7) | <.001 |
| 10-y CHD UKPDS risk score | 18.5 (12.2) | 17.8 (12.0) | .08 | 19.5 (13.3) | 15.8 (10.4) | <.001 | −3.1 (−4.2 to −2.0) | <.001 |
| 10-y fatal CHD UKPDS risk score | 12.1 (10.3) | 11.9 (10.2) | .82 | 12.8 (11.1) | 10.2 (8.5) | <.001 | −2.4 (−3.3 to −1.5) | .01 |
| Diet alone, No. (%) | 22 (8.0) | 18 (6.5) | .13 | 25 (8.7) | 21 (7.3) | .22 | | .85 |
| Medications, No. (%) | | | | | | | | |
| OHAs | 230 (83.6) | 232 (84.4) | .82 | 236 (81.9) | 240 (83.3) | .42 | NA | .85 |
| Sulfonylureas | 86 (31.3) | 85 (30.9) | >.99 | 72 (26.7) | 72 (25.0) | .36 | NA | .12 |
| Meglitinides | 27 (9.8) | 38 (13.8) | .007 | 29 (10.1) | 31 (10.8) | .69 | NA | .047 |
| Metformin | 200 (72.7) | 207 (75.3) | .17 | 213 (74.0) | 216 (75.0) | .61 | NA | .98 |
| Thiazolidinediones | 24 (8.7) | 40 (14.5) | .001 | 28 (9.7) | 47 (16.3) | <.001 | NA | .88 |
| Acarbose | 4 (1.5) | 4 (1.5) | >.99 | 5 (1.7) | 5 (1.7) | >.99 | NA | .95 |
| Insulin | 13 (4.7) | 16 (5.8) | .45 | 18 (6.3) | 18 (6.3) | >.99 | NA | .51 |
| Combined (OHA + insulin) | 22 (8.0) | 32 (11.6) | .006 | 19 (6.6) | 25 (8.7) | .11 | NA | .30 |
| Antihypertensive agents | 167 (60.7) | 181 (65.8) | .001 | 194 (67.4) | 191 (66.3) | .51 | NA | .004 |
| ACE inhibitors | 79 (28.7) | 85 (30.9) | .21 | 98 (34.0) | 93 (32.3) | .18 | NA | .06 |
| Angiotensin II receptor antagonists | 82 (29.8) | 93 (33.8) | .02 | 75 (26.0) | 75 (26.0) | >.99 | NA | .03 |
| Diuretics | 63 (22.9) | 71 (25.8) | .04 | 73 (25.3) | 67 (23.3) | .11 | NA | .007 |
| Calcium channel blockers | 32 (11.6) | 35 (12.7) | .25 | 51 (17.7) | 55 (19.1) | .29 | NA | .64 |
| β-Blockers | 37 (13.5) | 48 (17.5) | .003 | 50 (17.4) | 56 (19.4) | .11 | NA | .35 |
| $\alpha_1$-Blockers | 10 (3.6) | 10 (3.6) | >.99 | 13 (4.5) | 13 (4.5) | >.99 | NA | .91 |
| Lipid-lowering agents | 117 (42.5) | 148 (53.8) | <.001 | 116 (40.3) | 130 (45.1) | .003 | NA | .42 |
| Statins | 102 (37.1) | 130 (47.3) | .001 | 92 (31.9) | 107 (37.2) | <.001 | NA | .04 |
| Fibrates | 13 (4.7) | 17 (6.2) | .42 | 16 (5.6) | 18 (6.3) | .69 | NA | .72 |
| Omega-3 | 18 (6.5) | 21 (7.6) | .61 | 18 (6.3) | 20 (6.9) | .75 | NA | .77 |

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CI, confidence interval; CON, control group; DBP, diastolic blood pressure; EXE, exercise group; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MET-h/wk, metabolic equivalent hours per week; NA, not applicable; OHAs, oral hypoglycemic agents; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UKPDS, United Kingdom Prospective Diabetes Study; $\dot{V}O_{2max}$, maximal oxygen consumption.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; TG to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, multiply by 0.0259; and hs-CRP to nanomoles per liter, multiply by 9.524.

[a] Values are given as mean (SD) unless otherwise specified.

[b] Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables (medication use).

[c] Unpaired *t* test or Mann-Whitney test for continuous variables and logistic regression adjusted for baseline for categorical variables (medication use).

[d] Total PA = nonsupervised conditioning PA + supervised PA.

equivalent), traction movement on the frontal plane (lateral pull down or equivalent), squat movement (leg press or equivalent), trunk flexion for the abdominals, and 3 stretching positions. Intensity was adjusted according to improvements in predicted $\dot{V}O_{2max}$ and 1-repetition maximum, as recorded throughout the study. In addition, caloric expenditure was increased progressively by 0.1-kcal/kg body weight per session every month.

## OUTCOMES

The primary outcome was $HbA_{1c}$ level reduction. Secondary outcomes included other modifiable risk factors, dosage of glucose-, lipid-, and BP-lowering drugs, and global coronary heart disease (CHD) 10-year risk.[23]

**Table 2. Percentage of Subjects On-Target for Traditional Cardiovascular Risk Factors at Baseline and at the End of the 12-Month Study Period and Probability of Reaching These Targets and Percentage of Subjects According to the Number of Targets Reached at 12 Months**

| Target | CON, Baseline, % | CON, 12 mo, % | *P* Value, 0-12 mo[a] | EXE, Baseline, % | EXE, 12 mo, % | *P* Value, 0-12 mo[a] | OR (95% CI),[b] EXE vs CON |
|---|---|---|---|---|---|---|---|
| $HbA_{1c}$ <6.5% | 37.8 | 37.1 | .89 | 39.2 | 49.7 | .001 | 2.0 (1.3-3.1) |
| TG <150 mg/dL | 69.1 | 66.2 | .39 | 76.4 | 72.9 | .30 | 1.2 (0.8-1.8) |
| TC <175 mg/dL | 25.5 | 37.1 | .002 | 25.3 | 40.3 | <.001 | 1.2 (0.8-1.6) |
| HDL-C >40 mg/dL | 62.2 | 66.9 | .111 | 59.0 | 76.0 | <.001 | 2.0 (1.3-3.0) |
| LDL-C <100 mg/dL | 21.2 | 34.1 | <.001 | 16.2 | 41.5 | <.001 | 1.5 (1.1-2.2) |
| SBP <130 mm Hg | 18.2 | 26.5 | .005 | 22.0 | 37.3 | <.001 | 1.6 (1.1-2.4) |
| DBP <80 mm Hg | 16.7 | 22.5 | .072 | 18.1 | 26.5 | .002 | 1.2 (0.8-1.9) |
| **No. of Targets[c]** | **0** | **1** | **2** | **3** | **4** | **5** | |
| CON, % | 10.6 | 29.9 | 31.0 | 21.5 | 4.7 | 2.2 | |
| EXE, % | 3.9 | 20.1 | 36.7 | 21.9 | 15.5 | 1.8 | |

Abbreviations: CI, confidence interval; CON, control group; DBP, diastolic blood pressure; EXE, exercise group; $HbA_{1c}$, hemoglobin $A_{1c}$; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert TG to millimoles per liter, multiply by 0.0113; and to convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] McNemar test.

[b] Adjusted for baseline status (on target vs not on target), treatment at baseline, and change during the study.

[c] Targets considered: $HbA_{1c}$ level lower than 6.5%, HDL-C level higher than 40 mg/dL, LDL-C level lower than 100 mg/dL, SBP lower than 130 mm Hg, and DBP lower than 80 mm Hg.

## MEASUREMENTS

### Volume of PA

At baseline, the volume of PA was assessed retrospectively using the Minnesota leisure time PA questionnaire. The amount of nonsupervised PA was prospectively evaluated throughout the study by asking patients to fill in a daily diary, which was preliminarily validated by test-retest reliability. This diary considered the list of PAs coded in the Minnesota questionnaire; these activities were divided in conditioning or voluntary (corresponding to leisure time PA) and nonconditioning or nonvoluntary (including commuting, occupational, and home activities),[25] since conditioning PA consisted mainly of walking, running, and biking, for which estimates of metabolic equivalents (METs) are reliable, unlike nonconditioning PA. Volume was calculated by multiplying the MET scores corresponding to each Minnesota code[26] by time spent in each activity. For aerobic exercise, energy expenditure during supervised sessions was calculated automatically by the machines from workload using standard equations.[24] For resistance exercise, a conservative estimate of 3 MET-hours was established, based on direct measurements in subjects with T2DM not participating in this study.[27]

### Cardiovascular Risk Factors

The following modifiable cardiovascular risk factors were evaluated at baseline and end of study: $HbA_{1c}$, fasting blood glucose, and serum insulin levels; Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index; waist circumference; body mass index (BMI); BP; and triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hs-CRP) levels. Biochemical tests were performed at the central laboratory (at baseline and end of study) and locally (during the study period) to adjust treatment regimen.[23] Global CHD 10-year risk scores were calculated using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine.[28]

### Physical Fitness and Adverse Events

Cardiorespiratory fitness, strength, and flexibility (see eAppendix 2) were evaluated at baseline and end of study and also, in the EXE group, during the study period, to adjust training loads.[23] Assessment of cardiorespiratory fitness consisted of a submaximal $\dot{V}O_{2max}$ evaluation, ie, at 80% of the predicted maximal heart rate. All patients performed the test at the treadmill, using a modified Balke and Ware protocol (eTable 1), with direct measurement of oxygen consumption using the gas exchange analyzer FitMate (Cosmed, Rome, Italy) and concurrent assessment of heart rate. For strength assessment, though the 1-repetition maximum is the most reliable test, we used a maximal repetition (or 5- to 8-repetition maximum) test, which is preferable in patients with a low-fitness profile for safety reasons, and then predicted 1-repetition maximum using the Brzycki formula.[29] For hip and trunk flexibility assessment, a standard bending test was performed.

Adverse events were reported at intermediate visits and also, for EXE subjects, at supervised sessions, by completing a standard form.

## STATISTICAL ANALYSIS

Sample size calculation considered an $HbA_{1c}$ level reduction of at least 0.5% in EXE vs CON group with a standard deviation for baseline $HbA_{1c}$ of 1.6 and a statistical power of 90% ($\alpha = .05$). To this end, 215 patients per arm needed to be enrolled (430 total). A sample size of 606 patients allowed for a dropout rate of up to 25%.[23]

The $\chi^2$ test for categorical variables and the unpaired, 2-tailed *t* test or the corresponding nonparametric Mann-Whitney test for continuous variables were used to compare patients' characteristics at baseline. The efficacy of intervention on primary and secondary end points was assessed using the unpaired *t* test or the Mann-Whitney test for continuous variables, by comparing between-group changes from baseline to end of study. For categorical variables (ie, medications), logistic regression

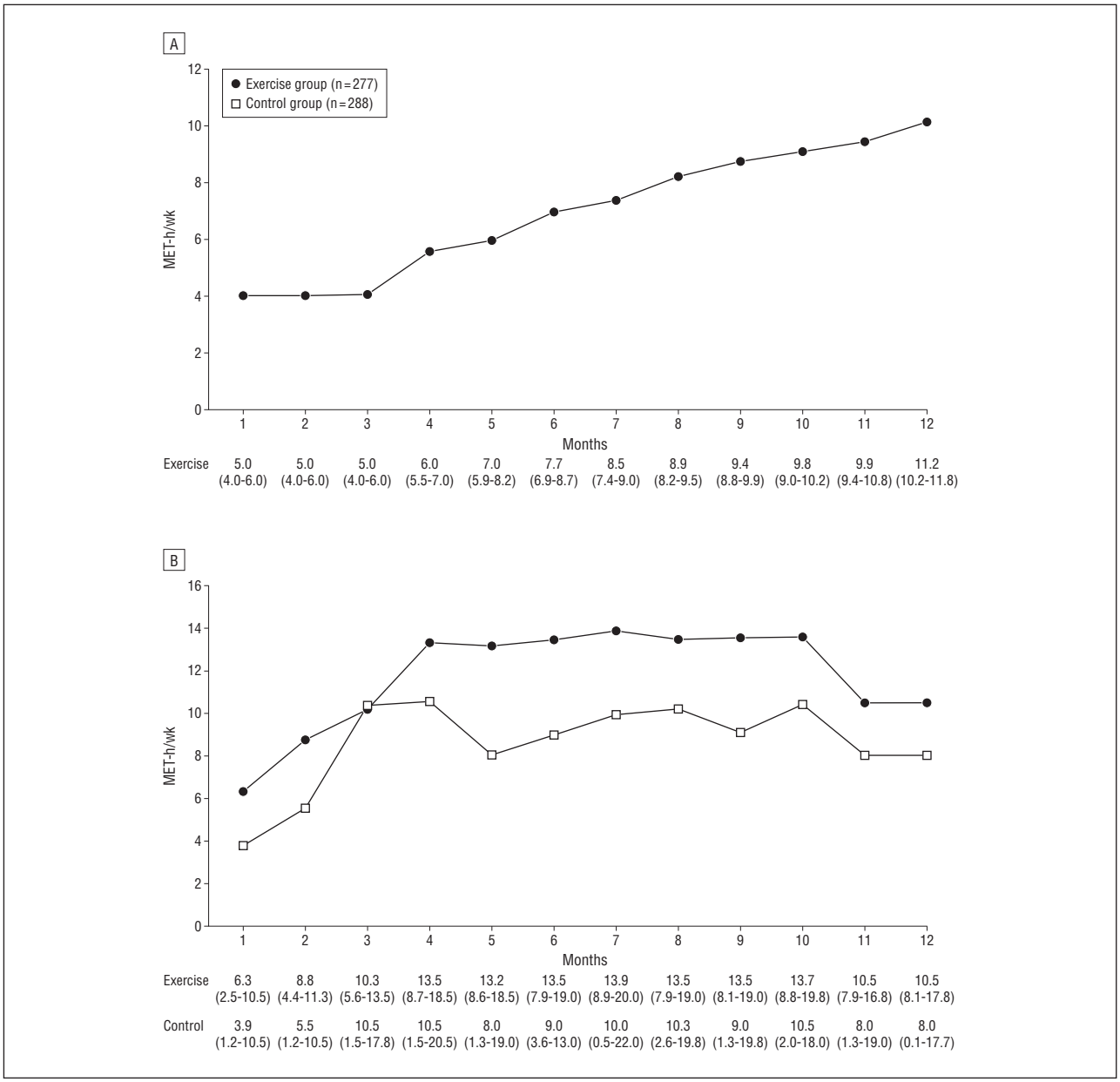


**Figure 2.** Average monthly energy expenditure from supervised exercise (A) and nonsupervised conditioning physical activity (B). Data are given as median (interquartile range); significantly different in exercise (EXE) vs control (CON) group at $P < .001$ by repeated-measures ANOVA (analysis of variance).

analysis was applied, with end-of-study rate of use included in the model as the dependent variable and baseline rate of use and study arm included as covariates.

To account for change in medication throughout the 12-month period, we performed both multiple regression and sensitivity analyses. In the regression models, the dependent variable was represented by baseline to end-of-study changes. Treatment at baseline and treatment initiation during the study were included in the model as dichotomous variables (yes vs no), whereas drug dosage was not taken into consideration. Sensitivity analysis was conducted for $HbA_{1c}$ and LDL-C by comparing study arms after excluding patients in whom treatment was modified for diabetes (ie, patients previously on diet alone who started treatment with oral agents, or patients receiving oral agents who added another oral agent or started insulin treatment) or statin therapy, respectively.

Within-group end-of-study vs baseline values were compared using the McNemar test for categorical variables and the Wilcoxon signed rank test for continuous variables. To identify independent predictors of $HbA_{1c}$ level changes from baseline, a multiple regression analysis was applied, with mean value of METs, baseline $HbA_{1c}$ values, sex, age, and changes in HOMA-IR, BMI, waist circumference, and TC, LDL-C, and HDL-C, and hs-CRP levels as covariates forced in the model.

The likelihood to achieve IDF targets[30] after 12 months according to study group, independent of volume, was estimated using a separate logistic regression model for each target (dependent variable), with study arm, baseline status (on target vs not on target), baseline mean value, and PA volume quintiles as covariates. Additional logistic analyses were performed to evaluate the likelihood of reaching specific targets according to PA volume. In these analyses, individual targets were the dependent variable, with PA volume quintiles, baseline status, baseline mean value, treatment at baseline, and change during the study as covariates. Results of these analyses were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A test for linear trend was also applied.

All analyses were performed on individuals completing the follow-up; an analysis with baseline values carried forward was also applied.

## RESULTS

The 2 study groups were similar for baseline characteristics (Figure 1 and eTable 2), including fitness, anthropometric, and biochemical parameters (**Table 1**), medications, and the percentage of subjects on-target for cardiovascular risk factors (**Table 2**). The median exercise training attendance was 80.3% (interquartile range, 75% to 99%) for aerobic and/or resistance sessions. During the 12-month period, 28 CON subjects and 15 EXE subjects dropped out (Figure 1). The results presented herein refer to patients completing the follow-up, since the baseline values carried forward analysis did not change the estimates.

According to the training program, energy expenditure during the exercise sessions increased progressively throughout the study (**Figure 2**A). In both groups, counseling promoted a marked increase in self-reported conditioning PA, which reached a peak at 4 months (Figure 2B) and was mainly aerobic. Energy expenditure from conditioning but not nonconditioning PA was significantly higher in EXE vs CON subjects, and the difference between the 2 groups became much larger when considering total volume of PA (nonsupervised conditioning plus supervised). This was associated with significantly more marked changes over baseline in the EXE vs CON group in cardiorespiratory fitness, upper and lower body strength, and flexibility (Table 1).

Reduction in the primary end point of $HbA_{1c}$ level was significantly higher in EXE than in CON subjects, with a 0.42% decrease in the former vs a nonsignificant 0.13% reduction in the latter group (Table 1). At multiple regression analysis, independent predictors of $HbA_{1c}$ level reduction were changes over baseline in waist circumference ($\beta = 0.04$; $P < .001$) HOMA-IR ($\beta = 0.053$; $P < .001$); male sex ($\beta = -0.17$; $P = .03$); older age ($\beta = -0.015$; $P = .001$); and higher baseline $HbA_{1c}$ level ($\beta = -0.47$; $P < .001$). In keeping with this, when patients were stratified by baseline $HbA_{1c}$ level, the extent of $HbA_{1c}$ level reduction increased progressively with the initial $HbA_{1c}$ value (eTable 3).

Changes over baseline in the EXE group were significantly more marked than in the CON group also for HOMA-IR; serum insulin level; systolic and diastolic BP; TC, HDL-C, and LDL-C levels; waist circumference; BMI, hs-CRP level; and total and fatal CHD 10-year risk scores. In fact, at 12 months, the EXE subjects exhibited significant improvements in all these parameters, whereas the CON participants showed significant decreases only in fasting blood glucose level, waist circumference, BP, and TC and LDL-C levels (Table 1).

During the study period, the percentage of patients reducing drug number and/or dosage was significantly higher in the EXE than in the CON group. In more detail, 13.5% of subjects in the EXE group vs none in the CON group stopped insulin therapy, while 5.1% in the EXE group vs 2.6% in the CON group reduced the number of oral agents without starting insulin therapy. The mean (SD) dose of insulin (+11.6 [4.6] IU/d vs –2.3 [1.9] IU/d in the EXE group) and the median dose of metformin (from 1700 [interquartile range, 1200-2550] mg/d to 2000 [1500-2712] mg/d vs no change) increased only in the CON group. In addition, the percentage of subjects requiring meglitinides, combined oral plus insulin therapy, and antihypertensive treatment (particularly angiotensin II receptor antagonists and diuretics) increased only in the CON group, whereas the percentage of those receiving statins increased significantly more in the CON than in the EXE group (Table 1). Finally, adjusted multiple linear regression analysis and sensitivity analysis confirmed differences between groups. In particular, multiple regression analysis after adjusting for baseline LDL-C level and treatment at baseline and throughout study with statins (the only medication that changed significantly in both groups) showed that patients assigned to the EXE group still had significantly reduced LDL-C levels compared with the CON group (mean [SE] difference, –10.0 [2.56] mg/dL; $P < .001$). Moreover, sensitivity analysis showed results superimposable to those obtained in the whole cohort for $HbA_{1c}$ (mean [SE] difference, –0.26% [0.10%]; $P = .03$) and LDL-C (mean [SE] difference, –10.95 [3.403] mg/dL; $P = .001$) outcomes.

At the end of the study, the percentage of subjects on-target according to the IDF Guidelines[30] increased significantly for TC and LDL-C levels and systolic BP in the CON group and for all cardiovascular risk factors, except triglycerides, in the EXE group. Overall, the probability of reaching all targets (except triglycerides) and the number of targets reached were higher in the EXE than in the CON subjects (Table 2). When adjusting for baseline values and volume of PA, patients assigned to the EXE arm still had a higher probability of reaching targets (**Table 3**).

The probability of reaching specific targets according to quintiles of PA volume showed a variable trend

**Table 3. Likelihood of Reaching Specific Targets According to Study Group, Independent of Volume of Physical Activity**

| Target | OR (95% CI),[a] EXE vs CON |
|---|---|
| $HbA_{1c}$ <6.5% | 2.0 (1.3-3.3) |
| $HbA_{1c}$ reduction ≥0.5 | 1.4 (0.9-2.3) |
| TG <150 mg/dL | 1.1 (0.7-1.8) |
| TC <175 mg/dL | 1.0 (0.6-1.4) |
| HDL-C >40 mg/dL | 1.9 (1.1-3.1) |
| LDL-C <100 mg/dL | 1.3 (0.9-2.0) |
| SBP <130 mm Hg | 1.4 (0.9-2.2) |
| DBP <80 mm Hg | 1.0 (0.6-1.6) |
| BMI reduction ≥1 | 2.0 (1.3-3.0) |
| Waist circumference reduction ≥5 cm | 2.7 (1.7-4.3) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CON, control group; DBP, diastolic blood pressure; EXE, exercise group; $HbA_{1c}$, hemoglobin $A_{1c}$; OR, odds ratio; SBP, systolic blood pressure; TG, triglycerides.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; TG to millimoles per liter, multiply by 0.0113; and cholesterol to millimoles per liter, multiply by 0.0259.

[a] Adjusted for baseline status (on-target vs not-on-target), baseline mean values and PA volume quintiles (conditioning + supervised PA [metabolic equivalent hours per week]).

**Table 4. Likelihood of Reaching Specific Targets According to Physical Activity (PA) Volume Quintiles[a]**

| Target | PA Volume Quintile[b] First Quintile (RC) (≤4.74) | Second Quintile (4.75-12.28) | Third Quintile (12.29-18.20) | Fourth Quintile (18.21-24.63) | Fifth Quintile (>24.63) | *P* Value for Trend |
|---|---|---|---|---|---|---|
| $HbA_{1c}$ <6.5% | 1 [Reference] | 1.3 (0.7-2.6) | 2.6 (1.3-5.0) | 2.1 (1.1-4.1) | 1.5 (0.8-2.9) | .13 |
| $HbA_{1c}$ reduction ≥0.5 | 1 [Reference] | 2.8 (1.2-6.4) | 5.1 (2.3-11.3) | 5.3 (2.4-11.4) | 4.6 (2.1-10.0) | .02 |
| TG <150 mg/dL | 1 [Reference] | 1.5 (0.8-2.9) | 1.4 (0.7-2.6) | 1.9 (1.0-3.6) | 1.4 (0.7-2.6) | .23 |
| TC <175 mg/dL | 1 [Reference] | 1.3 (0.7-2.2) | 1.2 (0.7-2.0) | 1.3 (0.8-2.3) | 1.7 (1.0-3.0) | .93 |
| HDL-C >40 mg/dL | 1 [Reference] | 1.5 (0.7-3.0) | 3.0 (1.4-6.1) | 2.6 (1.3-5.2) | 2.9 (1.4-6.0) | .30 |
| LDL-C <100 mg/dL | 1 [Reference] | 1.4 (0.8-2.5) | 1.4 (0.8-2.5) | 1.5 (0.8-2.6) | 2.0 (1.1-3.5) | .65 |
| SBP <130 mm Hg | 1 [Reference] | 2.0 (1.0-4.0) | 2.4 (1.2-4.8) | 3.0 (1.5-5.9) | 2.2 (1.1-4.4) | .05 |
| DBP <80 mm Hg | 1 [Reference] | 1.2 (0.6-2.5) | 2.2 (1.1-4.3) | 1.9 (1.0-3.8) | 1.6 (0.8-3.1) | .33 |
| BMI reduction ≥1 | 1 [Reference] | 1.8 (1.0-3.2) | 1.8 (1.0-3.3) | 2.6 (1.4-4.7) | 3.1 (1.7-5.6) | <.001 |
| Waist circumference reduction ≥5 cm | 1 [Reference] | 6.5 (2.4-18.0) | 9.1 (3.3-24.7) | 13.2 (4.9-35.7) | 15.9 (5.9-43.2) | <.001 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; $HbA_{1c}$, hemoglobin $A_{1c}$; RC, reference category; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; TG to millimoles per liter, multiply by 0.0113; and cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are given as odd ratios (95% confidence intervals), adjusted for baseline status, baseline mean value, treatment at baseline, and change during the study.

[b] Conditioning + supervised PA (metabolic equivalent hours per week).

**Table 5. Baseline to End-of-Study Changes (Δ) in Total and Fatal CHD UKPDS 10-Year Risk Scores According to Physical Activity (PA) Volume Quintiles**

| UKPDS Score | PA Volume Quintile[a] First Quintile (RC) (<4.74) | Second Quintile (4.74-12.28) | Third Quintile (12.29-18.20) | Fourth Quintile (18.21-24.63) | Fifth Quintile (>24.63) | *P* Value for Trend[c] |
|---|---|---|---|---|---|---|
| ΔTotal CHD[b] | 0.6 (−1.9 to 2.6) | −0.4 (−3.4 to 2.7) | −1.8 (−4.0 to −0.1) | −3.0 (−6.5 to −0.3) | −3.1 (−7.5 to −0.05) | <.001 |
| *P* value | | .11 | <.001 | <.001 | <.001 | |
| ΔFatal CHD[b] | 0.8 (−1.2 to 2.1) | −0.1 (−1.9 to 1.7) | −0.9 (−2.6 to 0.3) | −1.6 (−4.6 to 0.0) | −1.5 (−5.2 to 0.1) | <.001 |
| *P* value | | .09 | <.001 | <.001 | <.001 | |

Abbreviations: CHD, coronary heart disease; RC, reference category; UKPDS, United Kingdom Prospective Diabetes Study.

[a] Conditioning + supervised PA (metabolic equivalent hours per week).

[b] Median and interquartile range.

[c] Mann-Whitney test.

for the different risk factors (**Table 4**) and CHD scores (**Table 5**), without a clear dose-dependent effect, except for BMI, waist circumference, and CHD scores.

Adverse effects related to PA were more frequent, though not significantly, in EXE than in CON subjects, whereas the number of unrelated events did not differ between the 2 groups (**Table 6**). No episode of hypoglycemia was severe enough to require assistance.

## COMMENT

Mortality is inversely related to cardiorespiratory fitness and its main determinant PA, both in the general population and in subjects with T2DM.[1-3] However, evidence of efficacy of supervised exercise intervention on modifiable cardiovascular risk factors in patients with T2DM is mainly derived from small-sized studies,[18,19] and it is unclear which volume of exercise or PA is required to reduce cardiovascular burden and which is the best strategy for promoting PA in these high-risk individuals. The IDES showed that both the volume of PA and the extent of reduction of $HbA_{1c}$ level and other modifiable cardiovascular risk factors were significantly higher with the combination of structured exercise counseling and a prescribed and supervised training program than with counseling alone. Though difference in volume of PA between the 2 groups seems to explain the different outcome in terms of cardiovascular risk profile, the volume-adjusted analysis given in Table 3 suggests that the intervention strategy might have contributed to reduce modifiable cardiovascular risk factors and CHD scores. This effect might be attributed to supervision and/or type of exercise, though energy expenditure from resistance training was only a small part of total volume.

Important new information can be derived from these results. First, this study, which was multicenter and thus less dependent on local factors and of larger size and longer duration than previously published exercise intervention trials in patients with T2DM, provides definitive evidence that exercise is highly effective in improving $HbA_{1c}$ level and cardiovascular risk profile in these subjects. Second, supervised exercise programs could represent an effective strategy for promoting lifestyle changes in subjects with sedentary habits, such as patients with T2DM. In fact, supervised training on top of structured coun-

**Table 6. Adverse Events in the Control (CON) and Exercise (EXE) Groups**

| Events | CON | EXE | *P* Value[a] |
|---|---|---|---|
| Related to exercise intervention | 20 | 34 | .13 |
| Shoulder pain/chronic tendinopathy of rotator cuff | 5 | 9 | |
| (Aggravation of ) low back pain | 2 | 6 | |
| Aggravation of pre-existing osteoarthritis of hip or knee joint | 2 | 5 | |
| Shin splints/lower limb pain | 3 | 7 | |
| Other/generalized musculoskeletal discomfort | 8 | 7 | |
| Unrelated to exercise intervention | 23 | 25 | .90 |
| Elective surgery | 14 | 13 | .91 |
| Arthroscopic knee surgery | 1 | 2 | |
| Total thyroidectomy | 1 | 0 | |
| Cataract surgery | 3 | 2 | |
| Knee/hip joint replacement | 1 | 2 | |
| Inguinal hernia | 2 | 1 | |
| Varicose vein surgery | 1 | 2 | |
| Percutaneous coronary revascularization | 2 | 2 | |
| Mastectomy for carcinoma of the mammary gland | 2 | 1 | |
| Percutaneous lower limb revascularization | 1 | 1 | |
| Other serious medical event | 8 | 11 | .73 |
| Atrial fibrillation | 1 | 1 | |
| Newly diagnosed myocardial ischemia | 1 | 3 | |
| Accidental bone fracture | 2 | 3 | |
| Bronchitis/pneumonia | 3 | 2 | |
| Otitis | 1 | 2 | |
| Death from any cause | 1 | 1 | |
| Death from cardiovascular causes | 0 | 0 | |
| **Total** | **43** | **59** | .26[a] |

[a] $\chi^2$ test.

seling was superior to counseling alone in increasing the amount of nonsupervised PA, thus suggesting that the twice-a-week sessions supervised by an exercise specialist served as continuous reinforcement to counseling. In addition, these results might imply that the amount of PA that is required to effectively reduce cardiovascular burden in these high-risk subjects could be higher than the minimum recommended. This suggestion derives from the finding that counseling alone, though almost successful in achieving the currently recommended amount of PA (ie, 150 min/wk of moderate-intensity activity corresponding to 11.25 MET-h/wk) and improving significantly cardiorespiratory fitness in previously sedentary subjects, produced limited benefits in terms of glycemic control and reduction of global cardiovascular risk, at least over 1 year. Indeed, the currently recommended level of energy expenditure was originally derived from studies in healthy subjects and extended to the diabetic or IGT population, based on the amount of exercise performed (1) in the small-sized studies included in a meta-analysis,[18] which did not consider the volume of PA performed outside the exercise sessions, and (2) in the Diabetes Prevention Program (DPP),[9] in which the intensive lifestyle intervention consisted of a combination of exercise and diet. Besides, in the DPP,[11] the intensive lifestyle intervention, while greatly reducing the T2DM incidence compared with placebo, produced improvements in BP and cholesterol levels that were of an order of magnitude similar to that observed in the CON group (and less than that detected in the EXE group), whereas reductions of weight and triglyceride levels were more marked, possibly reflecting the effect of diet.

The finding that the extent of $HbA_{1c}$ level reduction was less than in previous reports[18,20] may be explained by the lower baseline $HbA_{1c}$ level. Indeed, a larger reduction was documented in individuals with higher baseline $HbA_{1c}$ levels, in keeping with the observation that baseline BP levels and the extent of BP reduction were higher in our study than in the study by Sigal et al.[20]

Potential limitations of this trial are self-reported data of nonsupervised PA, change in medication, unblinded design, and effect of diet. Provided that the use of devices is not applicable to a large multicenter study population followed for 12 months, the prospective evaluation of PA by a daily diary greatly reduces the risk of inaccuracy of self-reporting questionnaires, as compared with retrospective assessment. Moreover, changes in medication during the study attenuated, if any, differences between groups, thus ruling out the possibility that better outcome in EXE subjects was related to modification of treatment regimen. In fact, in keeping with a previous report,[8] drug number and/or dosage was significantly reduced as a consequence of increased PA, but this effect was observed only in EXE subjects, whereas the percentage of subjects requiring an increment of treatment regimen increased solely or more markedly in CON participants. Furthermore, though it was impossible to keep assignment to supervised training hidden to both patients and physicians, sample analysis was blinded. Finally, though diet was not considered in data analysis, patients from both groups received specific dietary prescriptions, and adherence to diet was verified at intermediate visits. Future studies are needed to determine the optimal "dose" of exercise and PA in subjects with T2DM and to assess the applicability

### The Italian Diabetes and Exercise Study Investigators

**Diabetes Centers**

*Diabetes Division, Sant'Andrea Hospital, Rome:* Francesco Fallucca, MD, Giuseppe Pugliese, MD, PhD, Serena Missori, MD, Maria Cristina Ribaudo, MD, and Elena Alessi, MD; *Division of Endocrinology and Metabolism, National Geriatric Institute (I.N.R.C.A.), Rome:* Felice Strollo, MD, and Massimo Morè, MD; *Diabetes Unit, Villa San Pietro Hospital:* Pietro Alimonti, MD, Nicolina Di Biase, MD, and Filomena Lasaracina, MD; *Diabetes Unit, City Hospital of Civitavecchia:* Graziano Santantonio, MD; *Diabetes Prevention Center (ACISMOM), Latina:* Laura Cruciani, MD; *Diabetes Unit, "Triolo Zancla" Clinic, Palermo:* Mario Manunta, MD; *Research Center for Physical Activity in Diabetes, University of Catania:* Maurizio Di Mauro, MD; *Department of Experimental and Clinical Medicine, University of Catanzaro:* Giorgio Sesti, MD, and Concetta Irace, MD; *Diabetes Unit, City Hospital of Catanzaro:* Luigi Puccio, MD; *Division of Endocrinology and Metabolism, University of Foggia:* Mauro Cignarelli, MD, Vincenzo Nicastro, MD, and Sabrina Piemontese, MD; *Diabetes Unit (AID), Provincial Health Authority for Naples:* Gerardo Corigliano, MD, Ernesto Rossi, MD, and Marco Corigliano, MD; *Department of Internal Medicine, University of Perugia:* Pierpaolo De Feo, MD, and Cristina Fatone, MD; *Diabetes Unit, New Hospital of San Giovanni di Dio, Florence:* Cristiana Baggiore, MD, and Roberto Russo, MD; *Division of Diabetes and Metabolism, National Geriatric Institute (I.N.R.C.A), Ancona:* Massimo Boemi, MD, and Luigi Lanari, MD; *Diabetes Unit, City Hospital of Brescia:* Umberto Valentini, MD, and Angela Girelli, MD; *Diabetes Unit, City Hospital of Ravenna:* Paolo Di Bartolo, MD, and Francesca Pellicano, MD; *Diabetes Unit, City Hospital of Rimini:* Paolo Mazzuca, MD; *Diabetes Unit, City Hospital of Reggio Emilia:* Enrica Manicardi, MD; *Diabetes Unit, San G. Battista Hospital, Turin:* Alberto Bruno, MD; *Diabetes Unit, "Cà Foncello" Hospital, Treviso:* Maria Sambataro, MD; *Diabetes Clinic, Monterotondo, Rome:* Stefano Balducci, MD; *Department of Internal Medicine, San Paolo Hospital, University of Milan:* Antonio Pontiroli, MD, Marco Laneri, MD, and Anna Boggio, MD; and *Diabetes Unit, Belcolle Hospital, Viterbo:* Nunzio Zagari, MD

**Metabolic Fitness Centers**

*Center for Functional Assessment in Sport, Sant'Andrea Hospital, Rome:* Fredrick Fernando, Carla Iacobini, and Stefano Menini; *Health Care Team, Monterotondo:* Gianluca Balducci, Lorella Senigagliesi, and Enza Spinelli; *Athlos Club, Civitavecchia:* Alessandro Di Giovanni; *Metabolic Fitness, Latina:* Mariano Pineda; *DO-IN, Palermo:* Umberto Pandolfo; *The Wellness Center, Naples:* Ciro Giordano; *Elisir Club, Perugia:* Antonella Settequattrini; *Metagym, Florence:* Marco Gambacciani; *Fisioclub, Ancona:* Matteo Fabrizi; *Lifeplanet, Ravenna:* Adriano Ceccherini and Enrico Balducci; *Steven Sporting Club, Rimini:* Mirko Quattrini; *Center for Physiatrics and Sports Medicine VITALIA, Torino:* Massimo Massarini; *Pianeta Sport, Treviso:* Giuseppe Baggio; *Winner Clubs, Reggio Emilia:* Marco Fornari; *Millennium, Brescia:* Davide Violi; *GCube Fitness & Wellness, Viterbo:* Giancarlo Cherubini; *Zenith Center for Medicine, Foggia:* Fabio Mastelloni; *S.S. Free Studios UISP, Catanzaro:* Valeria Micali; *Research Center for Physical Activity in Diabetes, Catania:* Daniela Cilano and Simone Di Luciano; and *Centro "La fonte del Benessere," Milan:* Davide Canevari


of this intervention strategy to clinical practice, including analysis of cost-effectiveness.

In conclusion, twice-weekly, supervised, facility-based combined aerobic and resistance exercise had significant incremental benefits beyond those of exercise counseling alone in terms of promotion of PA and improvement of $HbA_{1c}$ level and cardiovascular risk profile in sedentary patients with T2DM.


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**Author Affiliations:** Diabetes Division (Drs Balducci, Alessi, F. Fallucca, and Pugliese) and Laboratory of Clinical Chemistry (Drs Cavallo, Cardelli, and S. Fallucca), Sant'Andrea Hospital, Rome, Italy; Department of Clinical and Molecular Medicine, Second Medical School, "La Sapienza" University, Rome (Drs Balducci, Cavallo, Cardelli, S. Fallucca, Alessi, F. Fallucca, and Pugliese); Metabolic Fitness Association, Monterotondo, Rome (Drs Balducci and F. Fallucca); Department of Sport Science, University of Padua, Padua, Italy (Dr Zanuso); Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy (Dr Nicolucci); and Department of Internal Medicine, University of Perugia, Perugia, Italy (Dr De Feo).
**Correspondence:** Giuseppe Pugliese, MD, PhD, Department of Clinical Sciences, "La Sapienza" University of Rome, Viale del Policlinico, 155-00161 Rome, Italy (giuseppe.pugliese@uniroma1.it).



**Author Contributions:** All authors had access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Balducci, Zanuso, Nicolucci, De Feo, F. Fallucca, and Pugliese. *Acquisition of data:* Balducci, Zanuso, Nicolucci, De Feo, F. Fallucca, and Pugliese. *Analysis and interpretation of data:* Balducci, Zanuso, Nicolucci, De Feo, Cavallo, Cardelli, S. Fallucca, Alessi, and Pugliese. *Drafting of the manuscript:* Pugliese. *Critical revision of the manuscript for important intellectual content:* Balducci, Zanuso, Nicolucci, De Feo, Cavallo, Cardelli, S. Fallucca, Alessi, and F. Fallucca. *Statistical analysis:* Nicolucci. *Obtained funding:* Balducci and F. Fallucca. *Administrative, technical, and material support:* Balducci and Zanuso. *Study supervision:* Balducci, Zanuso, and Pugliese. *Counseling and training:* De Feo. *Laboratory organization:* Cavallo and Cardelli. *Sample storage:* S. Fallucca and Alessi.
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